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(54) Title: METHODS FOR THE CONTROLLED DELIVERY OF CARBON DISULFIDE FOR THE TREATMENT OF INFLAMMATORY CONDITIONS

(57) Abstract

In accordance with the present invention, it is described for the first time that CS_2 is capable of directly inhibiting the activity of NFκB, without the need for any other active agents to be present. It is assumed, therefor, that the inhibitory effect of, for example, pyrrolidine dithiocarbamate and other dithiocarbamates on NFκB may simply be attributed to CS_2 released upon *in vivo* hydrolysis of dithiocarbamates rather than as a result of the action of the parental compound per se. Dithiocarbamates may therefore be considered as pro-drugs for CS_2 for the treatment of inflammatory conditions mediated via NFκB pathways. Thus, in accordance with the present invention, there are provided methods for the treatment of inflammatory conditions mediated by NFκB pathways, as well as novel compositions useful for such methods.

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Methods for the Controlled Delivery of Carbon Disulfide for the Treatment of Inflammatory Conditions

FIELD OF THE INVENTION

The present invention relates to methods for the treatment of inflammatory conditions and compositions useful therefor. In another aspect of the invention, methods are provided for simultaneously treating a pathological condition with a pharmacologically active agent and an adjuvant which prolongs the circulating lifetime thereof.

BACKGROUND OF THE INVENTION

Carbon disulfide (CS_2) is a chemical component of dithiocarbamates. During the past several decades, a number of clinical applications of dithiocarbamates have been reported in the published literature. For example, diethyldithiocarbamate, a metal chelator, has been used clinically for the treatment of nickel poisoning (see, for example, Sunderman, F. W., in Annals Clin. Research 3:182-185 (1971); Sunderman, F. W., in Annals Clin Lab Science 11:1-8 (1981)). Dithiocarb (i.e., diethyldithiocarbamate) has also been used for the treatment of HIV patients (see, for example, Reisinger, E. C. et al., in Lancet, 335:679-682 (1990); and Lang, J.M., et al., in Lancet 2(8613):702-706 (1988)). In addition, disulfirm, a derivative of dithiocarbamates, has been shown to be effective for the treatment of alcohol abuse (see, for example, Eneanya, D. I., et al., in Annu. Rev. Pharmacol. Toxicol., 21:575-596 (1981); and Haley, T. J., in Drug Metabol., Rev., 9:319-335 (1979)).

Since the 1940's, CS_2 has been widely used in the rayon viscose industry. During the 1940's through the 1960's, there were reports that viscose workers were exposed, for many years, to high levels of CS_2 (e.g., 100-300 ppm). Exposure to CS_2 at such high levels has been associated with increased risk of cardiovascular disease, ischemic heart disease mortality and adverse effects on the nervous and reproductive systems (see, for example, Price, B. et al., in Regulatory Toxicol. Pharmacol., 26, 119-128 (1997) and Reinhardt, F., et al., in Int. Arch. Occup. Environ. Health, 69:332-338 (1997)). Since the 1970's, however, these high levels of CS_2 exposure are no longer found in the workplace (see, for example, Price, B. et al., supra).

The safe exposure levels of CS_2 permitted by regulation have been determined to be in the range of 10-20 ppm (about 4-8 μM in the air; see, for example, Price, B., et al., supra and Reinhardt, F., et al., supra). The LD_{50} values for CS_2 in 20-day-old rats and 1-day-old rats have been estimated to be 1.55 grams/kg and 0.58 grams/kg, respectively (see, for example, Green and Hunter, in Toxicol. Appl. Pharmacol., 78:130-8 (1985)). Exposure of human volunteers to 10-20 ppm CS_2 for four consecutive periods of 50 minutes has been conducted to evaluate the pharmacokinetics and metabolism of CS_2 in the human body (see, for example, Rosier, J et al., in Int. Arch. Occup. Health 59:243-250 (1987)). However, no beneficial therapeutic effect was observed for CS_2.

In the human body, CS_2 is known to react with amino- or sulfhydryl groups of protein molecules (see, for example, Valentine, W. M. et al., in Chem. Res. Toxicol., 8:96-102 (1995)). Conjugation of CS_2 and glutathione forms 2-thiothiazolidine carboxylic acid (TTCA); the latter product can be quantitated by chromatographic methods. The levels of TTCA detected in the urine seem to correlate with

the in vivo level of CS_2 (see, for example, Simon and Nicot, in J. Chromatograpy, 620:47-53 (1993)).

Dithiocarbamates are known to be unstable in acidic media, especially when the pH falls below 7 (see, for example, Martens, T., et al., in J. Pharmaceut Sciences 82:379-383 (1993)). The decomposition of dithiocarbamates seems to proceed via a hydrogen ion-catalyzed reaction. For example, under acidic conditions, diethyldithiocarbamate is rapidly decomposed to ethylamine and carbon disulfide with no evidence of toxic hydrogen sulfide production (see, for example, Martens, T., et al., supra).

In 1966, dithiocarbamate derivatives were found to be protective against carbon tetrachloride (CCl_4)-induced liver injury (see, for example, Sakaguchi, H. et al., in Biochem. Pharmac., 15:756 (1966)). This protective action of dithiocarbamates was later attributed to CS_2, especially in the case of oral administration of dithiocarbamate, wherein CS_2 is released upon acid hydrolysis in the stomach (see, for example, Masuda and Nakayama, in Biochem Pharmacol., 31:2713-2725 (1982)). Subsequently, the oral administration of dithiocarbamate was shown to suppress the metabolism of many hepatotoxins such as aniline, p-nitroanisole, aminopyrine, 3,4-benzpyrene and CCl_4, as a result of interference by CS_2 with the bioactivation of hepatotoxins by the microsomal monooxygnease system (see, for example, Masuda and Nakayama, supra).

Schreck and colleagues in 1992 reported that dithiocarbamates were potent inhibitors of nuclear factor kappaB (NFκB), a multiprotein complex that controls the activation of a multitude of genes encoding signaling and inflammatory defense proteins (see, for example, Schreck, R., et al., in J. Exp. Med., 175:1181-1194 (1992)).

Despite the advent of modern pharmaceutical technology, many drugs still possess untoward toxicities which often limit the therapeutic potential thereof. For example, although non-steroid anti-inflammatory drugs (NSAIDs) are a class of compounds which are widely used for the treatment of inflammation, pain and fever, NSAIDs (e.g., aspirin, ibuprofen and ketoprofen) can cause gastrointestinal ulcers, a side-effect that remains the major limitation to the use of NSAIDs (see, for example, J. L. Wallace, in Gastroenterol. 112:1000-1016 (1997); A. H. Soll et al., in Ann Intern Med. 114:307-319 (1991); and J. Bjarnason et al., in Gastroenterol. 104:1832-1847 (1993)).

There are two major ulcerogenic effects of NSAIDs: (1) topical irritant effects on the epithelium of the gastrointestinal tract and (2) suppression of gastrointestinal prostaglandin synthesis. In recent years, numerous strategies have been attempted to design and develop new NSAIDs that reduce the damage to the gastrointestinal tract. These efforts, however, have largely been unsuccessful. For example, enteric coating or slow-release formulations designed to reduce the topical irritant properties of NSAIDs have been shown to be ineffective in terms of reducing the incidence of clinically significant side effects, including perforation and bleeding (see, for example, D. Y. Graham et al., in Clin. Pharmacol. Ther. 38:65-70 (1985); and J. L. Carson, et al., in Arch. Intern. Med., 147:1054-1059 (1987)).

Accordingly, there is still a need in the art for methods for the safe and effective treatment of inflammatory conditions, as well as methods to reduce the incidence of side-effects caused by such pharmacologically active agents as aspirin, ibuprofen, and the like.

BRIEF DESCRIPTION OF THE INVENTION

In accordance with the present invention, it is described for the first time that CS_2 is capable of directly inhibiting the activity of NFκB, without the need for any other active agents to be present. It is assumed, therefor, that the inhibitory effect of, for example, pyrrolidine dithiocarbamate and other dithiocarbamates on NFκB may simply be attributed to CS_2 released upon in vivo hydrolysis of dithiocarbamates rather than as a result of the action of the parental compound per se. Dithiocarbamates may therefore be considered as pro-drugs for CS_2 for the treatment of inflammatory conditions mediated via NFκB pathways.

Thus, in accordance with the present invention, there are provided methods for the treatment of inflammatory conditions mediated by NFκB pathways, as well as novel compositions useful for such methods.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 collectively presents uv-visible spectra of N-methyl-D-glucamine dithiocarbamate (MGD) under different pH conditions. Thus, MGD was dissolved in phosphate-buffered saline to a final concentration of 10 μM in either pH 7.4 (Figure 1A) or pH 4.0 (Figure 1B). Uv-visible spectra were recorded with a Hewlett-Packard Diode Array Spectrophotometer. Both the 258 nm and 286 nm peaks of MGD, which are prominent at pH 7.4, disappeared at pH 4.0, indicative of the cleavage of the amide bond of MGD at acidic pH. The 196 nm peak is assigned to carbon disulfide.

Figure 2 presents a plot of uninjected footpad severity scores versus time for L-proline dithiocarbamate treatment of adjuvant-induced arthritic rats. At day 7

after injection of adjuvant into the footpad, the rats were separated into two groups (18 animals in each group). One group received an oral administration of L-proline dithiocarbamate in drinking water at lib (10 mg/ml) and the other group drank distilled water at lib until day 14. The degree of swelling in the uninjected footpad was estimated by the severity scoring system as follows: 0, no redness or inflammation; 1, one area of redness or inflammation less than 2 mm in diameter; 2, two areas of redness or inflammation, each less than 2 mm in diameter; 3, partial redness and/or inflammation of the footpad; 4, redness and/or inflammation of substantially the entire footpad; 5, criteria of 4 plus at least one toe red/inflamed; and 6, criteria of 4 plus toes inflamed and deformed (i.e., toes curl under). Asterisks indicate statistically significant differences ($p<0.05$) in the severity scores between the treated animals and the controls.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with the present invention, there are provided methods for the treatment of inflammatory conditions mediated by nuclear factor kappa-B (NFκB). Invention methods comprise administering an effective amount of a therapeutic consisting essentially of carbon disulfide in a pharmaceutically acceptable carrier to a subject in need thereof.

In a particular aspect of the invention, the carbon disulfide is administered in a chemically protected form. Those of skill in the art can readily identify suitable chemically protected forms of carbon disulfide for use herein. A presently preferred source of carbon disulfide contemplated for use herein are dithiocarbamates which are readily hydrolyzable under selected physiological conditions.

As employed herein, the phrase "selected physiological conditions" refers to the physiological conditions typical of the site at which hydrolysis of dithiocarbamates is desired. For example, oral administration subjects the dithiocarbamate to the acidic conditions of the stomach, which induce hydrolysis of the administered dithiocarbamate.

Suitable readily hydrolyzable dithiocarbamate compounds contemplated for use in the practice of the present invention can be described with reference to generic structure I as follows:

$$[R_1R_2N\text{-}C(S)\text{-}S^-]_x\ M^{+1,\,+2,\,+3} \qquad (I)$$

wherein:

each of R_1 and R_2 is independently a C_1 up to C_{18} alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, acyl, substituted acyl, or

R_1 and/or R_2 is a divalent or polyvalent moiety, wherein said divalent or polyvalent moiety serves as the same substituent for two or more dithiocarbamate structures, thereby linking said structures together so as to form a bis(dithiocarbamate) or poly(dithiocarbamate) species,

x is 1 or 2, and

M is a monovalent cation when x is 1, or M is a physiologically compatible divalent or trivalent transition metal cation when x is 2.

Presently preferred dithiocarbamate compounds having generic structure I are those wherein:

R_1 and/or R_2 is a divalent moiety selected from the group consisting of alkylene, substituted alkylene, oxyalkylene,

substituted oxyalkylene, alkenylene, substituted alkenylene, arylene, substituted arylene, alkarylene, substituted alkarylene, aralkylene and substituted aralkylene, wherein said divalent moiety serves as the same substituent for two dithiocarbamate structures, thereby linking said structures together so as to form a bis(dithiocarbamate) species.

Additional preferred dithiocarbamate compounds having generic structure I are those wherein:

R_1 and/or R_2 is a polyvalent moiety, wherein said polyvalent moiety serves as the same substituent for a plurality of dithiocarbamate structures, thereby linking said structures together so as to form a poly(dithiocarbamate) species.

Still further preferred dithiocarbamate compounds having generic structure I are those wherein:

each of R_1 and R_2 = a C_1 up to C_{12} alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl or substituted alkynyl, wherein the substituents are selected from carboxyl, -C(O)H, oxyacyl, phenol, phenoxy, pyridinyl, pyrrolidinyl, amino, amido, hydroxy, nitro or sulfuryl, and

M = Fe^{+2} or Fe^{+3}.

Additional preferred dithiocarbamate compounds having generic structure I are those wherein:

R_1 is selected from a C_2 up to C_8 alkyl or substituted alkyl, wherein the substituents are selected from carboxyl, acetyl, pyridinyl, pyrrolidinyl, amino, amido, hydroxy or nitro, and

R_2 is selected from a C_1 up to C_8 alkyl or substituted alkyl, and

M = Fe^{+2}.

Still further preferred dithiocarbamate compounds having generic structure **I** are those wherein:

R_1 is selected from a C_2 up to C_6 alkyl or substituted alkyl, wherein the substituents are selected from carboxyl, acetyl, amido or hydroxy, and

R_2 is selected from a C_1 up to C_6 alkyl or substituted alkyl, and

M = Fe^{+2}.

Monovalent cations contemplated for incorporation into the above-described dithiocarbamate compounds include H^+, Na^+, NH_4^+, tetraalkyl ammonium, and the like. Physiologically compatible divalent or trivalent transition metal cations contemplated for incorporation into the above-described dithiocarbamate compounds include charged forms of iron, cobalt, copper, manganese, ruthenium, or the like (e.g., Fe^{+2}, Fe^{+3}, Co^{+2}, Co^{+3}, Cu^{+2}, Mn^{+2}, Mn^{+3} or Ru^{+3}). In accordance with the present invention, the ratio of dithiocarbamate-species to counter-ion M can vary widely. Thus, dithiocarbamates can be administered without any added metallic counter-ion (i.e., M = H^+, or a transition metal cation to dithiocarbamate-species ratio of zero), with ratios of transition metal cation to dithiocarbamate-species up to about 1:2 (i.e., a 2:1 dithiocarbamate:transition metal cation complex) being suitable.

As employed herein, "substituted alkyl" comprises alkyl groups further bearing one or more substituents selected from hydroxy, alkoxy (of a lower alkyl group), mercapto (of a lower alkyl group), cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, aryl,

substituted aryl, heteroaryl, substituted heteroaryl, aryloxy, substituted aryloxy, halogen, trifluoromethyl, cyano, nitro, nitrone, amino, amido, -C(O)H, acyl, oxyacyl, carboxyl, carbamate, sulfonyl, sulfonamide, sulfuryl, and the like.

As employed herein, "cycloalkyl" refers to cyclic ring-containing groups containing in the range of about 3 up to 8 carbon atoms, and "substituted cycloalkyl" refers to cycloalkyl groups further bearing one or more substituents as set forth above.

As employed herein, "cycloalkylene" refers to divalent ring-containing groups containing in the range of about 3 up to 8 carbon atoms, and "substituted cycloalkylene" refers to cycloalkylene groups further bearing one or more substituents as set forth above.

As employed herein, "alkylene" refers to saturated, divalent straight or branched chain hydrocarbyl groups typically having in the range of about 2 up to 12 carbon atoms, and "substituted alkylene" refers to alkylene groups further bearing one or more substituents as set forth above.

As employed herein, "alkenyl" refers to straight or branched chain hydrocarbyl groups having at least one carbon-carbon double bond, and having in the range of about 2 up to 12 carbon atoms, and "substituted alkenyl" refers to alkenyl groups further bearing one or more substituents as set forth above.

As employed herein, "alkenylene" refers to divalent straight or branched chain hydrocarbyl groups having at least one carbon-carbon double bond, and typically having in the range of about 2 up to 12 carbon atoms, and "substituted alkenylene" refers to alkenylene

groups further bearing one or more substituents as set forth above.

As employed herein, "alkynyl" refers to straight or branched chain hydrocarbyl groups having at least one carbon-carbon triple bond, and having in the range of about 2 up to 12 carbon atoms, and "substituted alkynyl" refers to alkynyl groups further bearing one or more substituents as set forth above.

As employed herein, "aryl" refers to aromatic groups having in the range of 6 up to 14 carbon atoms and "substituted aryl" refers to aryl groups further bearing one or more substituents as set forth above.

As employed herein, "alkylaryl" refers to alkyl-substituted aryl groups and "substituted alkylaryl" refers to alkylaryl groups further bearing one or more substituents as set forth above.

As employed herein, "arylalkyl" refers to aryl-substituted alkyl groups and "substituted arylalkyl" refers to arylalkyl groups further bearing one or more substituents as set forth above.

As employed herein, "arylalkenyl" refers to aryl-substituted alkenyl groups and "substituted arylalkenyl" refers to arylalkenyl groups further bearing one or more substituents as set forth above.

As employed herein, "arylalkynyl" refers to aryl-substituted alkynyl groups and "substituted arylalkynyl" refers to arylalkynyl groups further bearing one or more substituents as set forth above.

As employed herein, "arylene" refers to divalent aromatic groups typically having in the range of 6 up to 14

carbon atoms and "substituted arylene" refers to arylene groups further bearing one or more substituents as set forth above.

As employed herein, "alkarylene" refers to alkyl-substituted divalent aryl groups typically having in the range of about 7 up to 16 carbon atoms and "substituted alkarylene" refers to alkarylene groups further bearing one or more substituents as set forth above.

As employed herein, "aralkylene" refers to aryl-substituted divalent alkyl groups typically having in the range of about 7 up to 16 carbon atoms and "substituted aralkylene" refers to aralkylene groups further bearing one or more substituents as set forth above.

As employed herein, "aralkenylene" refers to aryl-substituted divalent alkenyl groups typically having in the range of about 8 up to 16 carbon atoms and "substituted aralkenylene" refers to aralkenylene groups further bearing one or more substituents as set forth above.

As employed herein, "aralkynylene" refers to aryl-substituted divalent alkynyl groups typically having in the range of about 8 up to 16 carbon atoms and "substituted aralkynylene" refers to aralkynylene groups further bearing one or more substituents as set forth above.

As employed herein, "heterocyclic" refers to cyclic (i.e., ring-containing) groups containing one or more heteroatoms (e.g., N, O, S, or the like) as part of the ring structure, and having in the range of 3 up to 14 carbon atoms and "substituted heterocyclic" refers to heterocyclic groups further bearing one or more substituents as set forth above.

As employed herein, "heterocycloalkylene" refers to divalent cyclic (i.e., ring-containing) groups containing one or more heteroatoms (e.g., N, O, S, or the like) as part of the ring structure, and having in the range of 3 up to 14 carbon atoms and "substituted heterocycloalkylene" refers to heterocycloalkylene groups further bearing one or more substituents as set forth above.

As employed herein, "aroyl" refers to aryl-carbonyl species such as benzoyl and "substituted aroyl" refers to aroyl groups further bearing one or more substituents as set forth above.

As employed herein, "acyl" refers to alkyl-carbonyl species.

As employed herein, "halogen" refers to fluoride, chloride, bromide or iodide atoms.

Diseases and conditions contemplated for treatment in accordance with the present invention include inflammatory conditions and infectious diseases, such as, for example, septic shock, hemorrhagic shock, anaphylactic shock, toxic shock syndrome, ischemia, cerebral ischemia, administration of cytokines, overexpression of cytokines, ulcers, inflammatory bowel disease (e.g., ulcerative colitis or Crohn's disease), diabetes, arthritis, asthma, Alzheimer's disease, Parkinson's disease, multiple sclerosis, cirrhosis, allograft rejection, encephalomyelitis, meningitis, pancreatitis, peritonitis, vasculitis, lymphocytic choriomeningitis, glomerulonephritis, uveitis, ileitis, inflammation (e.g., liver inflammation, renal inflammation, and the like), burn, infection (including bacterial, viral, fungal and parasitic infections), hemodialysis, chronic fatigue syndrome, stroke, cancers (e.g., breast, melanoma,

carcinoma, and the like), cardiopulmonary bypass, ischemic/reperfusion injury, gastritis, adult respiratory distress syndrome, cachexia, myocarditis, autoimmune disorders, eczema, psoriasis, heart failure, heart disease, atherosclerosis, dermatitis, urticaria, systemic lupus erythematosus, AIDS, AIDS dementia, chronic neurodegenerative disease, chronic pain, priapism, cystic fibrosis, amyotrophic lateral sclerosis, schizophrenia, depression, premenstrual syndrome, anxiety, addiction, migraine, Huntington's disease, epilepsy, neurodegenerative disorders, gastrointestinal motility disorders, obesity, hyperphagia, solid tumors (e.g., neuroblastoma), malaria, hematologic cancers, myelofibrosis, lung injury, graft-versus-host disease, head injury, CNS trauma, hepatitis, renal failure, liver disease (e.g., chronic hepatitis C), drug-induced lung injury (e.g., paraquat), myasthenia gravis (MG), ophthalmic diseases, post-angioplasty, restenosis, angina, coronary artery disease, and the like.

In accordance with another embodiment of the present invention, there are provided improved methods for the treatment of pathological conditions employing a pharmacologically active agent therefor, the improvement comprising administering said pharmacologically active agent as part of a therapeutic consisting essentially of said pharmacologically active agent and carbon disulfide in a pharmaceutically acceptable carrier.

In accordance with an alternate aspect of the present embodiment of the present invention, the therapeutic employed for carrying out the improved methods comprises said pharmacologically active agent, a physiologically compatible compound which is readily hydrolyzable under selected physiological conditions to release carbon disulfide, and a pharmaceutically acceptable carrier therefor.

Physiologically compatible compounds which are readily hydrolyzable under selected physiological conditions to release carbon disulfide include dithiocarbamates as described in detail hereinabove.

Pharmacologically active agents contemplated for administration in accordance with the present invention, i.e., in combination with carbon disulfide in a pharmaceutically acceptable carrier or a physiologically compatible compound which is readily hydrolyzable under selected physiological conditions to release carbon disulfide include:

NSAIDs, such as acetaminophen (Tylenol, Datril, etc.), aspirin, ibuprofen (Motrin, Advil, Rufen, others), choline magnesium salicylate (Triasate), choline salicylate (Anthropan), diclofenac (voltaren, cataflam), diflunisal (dolobid), etodolac (lodine), fenoprofen calcium (nalfon), flurobiprofen (ansaid), indomethacin (indocin, indometh, others), ketoprofen (orudis, oruvail), ketorolac tromethamine (toradol), magnesium salicylate (Doan's, magan, mobidin, others), meclofenamate sodium (meclomen), mefenamic acid (relafan), oxaprozin (daypro), piroxicam (feldene), sodium salicylate, sulindac (clinoril), tolmetin (tolectin), meloxicam, nabumetone, naproxen, lornoxicam, nimesulide, indoprofen, remifenzone, salsalate, tiaprofenic acid, flosulide, and the like;

analgesics/antipyretics (e.g., aspirin, acetaminophen, ibuprofen, naproxen sodium, buprenorphine hydrochloride, propoxyphene hydrochloride, propoxyphene napsylate, meperidine hydrochloride, hydromorphone hydrochloride, morphine sulfate, oxycodone hydrochloride, codeine phosphate, dihydrocodeine bitartrate, pentazocine

hydrochloride, hydrocodone bitartrate, levorphanol tartrate, diflunisal, trolamine salicylate, nalbuphine hydrochloride, mefenamic acid, butorphanol tartrate, choline salicylate, butalbital, phenyltoloxamine citrate, diphenhydramine citrate, methotrimeprazine, cinnamedrine hydrochloride, meprobamate, and the like);

sedatives/hypnotics (e.g., barbiturates (e.g., pentobarbital, pentobarbital sodium, secobarbital sodium), benzodiazapines (e.g., flurazepam hydrochloride, triazolam, tomazeparm, midazolam hydrochloride, and the like);

antianginal agents (e.g., beta-adrenergic blockers, calcium channel blockers (e.g., nifedipine, diltiazem hydrochloride, and the like), nitrates (e.g., nitroglycerin, isosorbide dinitrate, pentaerythritol tetranitrate, erythrityl tetranitrate, and the like));

antianxiety agents (e.g., lorazepam, buspirone hydrochloride, prazepam, chlordiazepoxide hydrochloride, oxazepam, clorazepate dipotassium, diazepam, hydroxyzine pamoate, hydroxyzine hydrochloride, alprazolam, droperidol, halazepam, chlormezanone, and the like);

antidepressants (e.g., doxepin hydrochloride, amoxapine, trazodone hydrochloride, amitriptyline hydrochloride, maprotiline hydrochloride, phenelzine sulfate, desipramine hydrochloride, nortriptyline hydrochloride, tranylcypromine sulfate, fluoxetine hydrochloride, doxepin hydrochloride, imipramine hydrochloride, imipramine pamoate, nortriptyline, amitriptyline hydrochloride, isocarboxazid, desipramine hydrochloride, trimipramine maleate, protriptyline hydrochloride, and the like);

antipsychotic agents (e.g., haloperidol, loxapine succinate, loxapine hydrochloride, thioridazine, thioridazine hydrochloride, thiothixene, fluphenazine hydrochloride, fluphenazine decanoate, fluphenazine enanthate, trifluoperazine hydrochloride, chlorpromazine hydrochloride, perphenazine, lithium citrate, prochlorperazine, and the like);

antimanic agents (e.g., lithium carbonate),

antiarrhythmics (e.g., bretylium tosylate, esmolol hydrochloride, verapamil hydrochloride, amiodarone, encainide hydrochloride, digoxin, digitoxin, mexiletine hydrochloride, disopyramide phosphate, procainamide hydrochloride, quinidine sulfate, quinidine gluconate, quinidine polygalacturonate, flecainide acetate, tocainide hydrochloride, lidocaine hydrochloride, and the like);

antihypertensive drugs, such as diuretics (hydrochlorothiazide, chlorthalidone, metolazone, indapamide, furosemide, bumetanide, torsemide, triamterene, amiloride, spronolactone), beta-adrenergic blocking agents (acebutolol, atenolol, betaxolol, cartelol, labetalol, metoprolol, nadolol, penbutolol, pindolol, propranolol, timolol), angiotensin converting enzyme inhibitors (benazepril, captopril, enalapril, fosinopril, quinoapril, ramimpril, losartan), calcium channel-blocking agents (diltiazem, verapamil, amlodipine, felodipine, isradipine, nicardipine, nifedipine), alpha-adrenoceptor blocking agents, sympatholytics, and vasodilators (such as prazosin, terazosin, doxazosin, clonidine, guanabenz, guanfacine, methylodopa, guanethidine, guanethidine monosulfate, reserpine, hydralazine, minoxidil, and the like), as well as agents such

as trimethaphan camsylate, phenoxybenzamine hydrochloride, pargyline hydrochloride, deserpidine, diazoxide, rescinnamine, sodium nitroprusside, rauwolfia serpentina, alseroxylon, phentolamine mesylate, and the like;

antihistamine/antipruritic drugs, such as ethanolamines (e.g., diphenhydramine, diphenhydramine hydrochloride, clemastine, clemastine fumarate, and the like), ethylenediamines (e.g., brompheniramine, brompheniramine maleate, chlorpheniramine, chlorpheniramine maleate, dexchlorpheniramine maleate, triprolidine, triprolidine hydrochloride, and the like), phenothiazines (e.g., promethazine), piperidines (e.g., hydroxzine, hydroxyzine hydrochloride, terfenadine, astemizole, azatadine, azatadine maleate, and the like), cyproheptadine, cyproheptadine hydrochloride, loratidine, carbinoxamine maleate, diphenylpyraline hydrochloride, phenindamine tartrate, tripelennamine hydrochloride, methdilazine hydrochloride, trimprazine tartrate, and the like;

immunosuppressants, such as glucocorticoids (methylprednisolone), myelin basic protein (e.g., 7-capaxone), anti-Fc receptor monoclonal antibodies, hydroorotate dehydrogenase inhibitor, anti-IL2 monoclonal antibodies (e.g., CHI-621 and dacliximab), buspirone, castanospermine, CD-59 (complement factor inhibitor), 5-lipoxygenase inhibitor (e.g., CMI-392), phosphatidic acid synthesis antagonists, ebselen, edelfosine, enlimomab, galaptin, platelet activating factor antagonists, selectin antagonists (e.g., ICAM-4), interleukin-10 agonist, macrocylic lactone, methoxatone, mizoribine, OX-19, peptigen agents, PG-27, protein kinase C inhibitors,

phosphodiesterase IV inhibitor, single chain antigen binding proteins, complement factor inhibitor, sialophorin, sirolimus, spirocyclic lactams, 5-hydroxytryptamine antagonist, anti-TCR monoclonal antibodies, CD5 gelonin and TOK-8801, and the like;

antimetabolite cytotoxics (azathioprine, cyclophosphamide), C5a release inhibitor, benzydamine, peldesine, pentostatin, SDZ-ASM-981, thalidomide, benzoporphyrin derivatives, arachidonate antagonists (e.g., halometasone, halobetasol propionate), corticosteriod (clobetasol propionate), growth hormone antagonists (octapeptide somatostatin analogue, lanreotide, angiopeptin and dermopeptin), thymopentin, and the like;

neuroprotective agents, such as α-adrenoreceptor antagonist (i.e, α-dihydroergocryptine), NMDA antagonists (e.g., 5,6,7-tichloro-THQTQ, remacemide, 2-piperazinecarboxylic acid, N-indologlycinamide derivatives, spiro[benzo(b)thiophen-4(5H) derivatives, CP-101606, eliprodil, dexanabinol, GV-150526, L-695902, L-701324, amantadine derivatives, dizocilpine, benzomorphan derivatives, aptiganel, (S)-α-phenyl-2-pyridine ethanamide dihyrochloride and 1-amino-cyclopentanecarboxylic acid), sodium channel antagonists (e.g., 619C89), glycine antagonists (e.g., glystasins), calcium channel antagonists (e.g., 3,5-pyridinedicarboxylic acid derivatives, conopeptides, 1-piperazineethanol, thieno[2,3-b]pyridine-5-carboxylic acid derivatives, NS-3034, nilvadipine, nisoldipine, tirilazad mesylate, 2H-1-enzopyran-6-ol, nitrone spin traps, iacidipine, iomeerzine hydrochloride, lemildipine, lifarizine, CPC-304, efonidipine, F-0401, piperazine derivatives), calpain

inhibitors, fibrinogen antagonists (e.g., ancrod), integrin antagonists (e.g., antegren), thromboxane A_2 antagonist (e.g., 9H-carbazole-9-propanoic acid derivatives, 5-Heptenoic acid derivatives and 1-azulenesulfonic acid derivatives), brain-derived neurotropic factor, adrenergic transmitter uptake inhibitor (e.g., 1-butanamine), endothelin A receptor antagonists (e.g., benzenesulfonamide derivatives, GABA A receptor antagonists (e.g., triazolopyrimidine derivatives and cyclohexaneacetic acid derivatives), GPIIb IIIa receptor antagonists (e.g., C68-22), platelet aggregation antagonist (e.g., 2(1H)-quinolinone derivatives, 1H-pyrrole-1-acetic acid derivatives and coumadin), Factor Xa inhibitor, CPC-211, corticotropin releasing factor agonist, thrombin inhibitor (e.g., cothrombins, fraxiparine, dermatan sulfate and heparinoid), dotarizine, intracellular calcium chelators (e.g., BAPTA derivatives), radical formation antagonists (EPC-K1, 3-pyridinecarboxamide derivatives, superoxide dismutase, raxofelast, lubeluzole, 3H-pyrazol-3-one derivatives, kynurenic acid derivatives, homopiperazine derivatives, and polynitroxyl albumin), protein kinase inhibitors (e.g., 1H-1,4-diazepine), nerve growth agonist (e.g., floor plate factor-5), glutamate antagonist (e.g., cyclohexanepropanoic acid, riluzole, NS-409 and acetamide derivatives), lipid peroxidase inhibitor (e.g., 2,5-cyclohexadiene-1,4-dione derivatives), sigma receptor agonist (e.g., cyclopropanemethanamine derivatives and SA-4503), thyrotropin releasing hormone agonist (e.g., JTP-2942, L-prolinamide and posatirelin), prolyl endopeptidase inhibitor,

monosialoganglioside GM1, proteolytic enzyme inhibitor (e.g., nafamostat), neutrophil inhibitory factor, platelet activating factor antagonist (e.g., nupafant), monoamine oxidase B inhibitor (e.g., parafluoroselegiline and benzonitrile derivatives), PARS inhibitors, Angiotensin I converting enzyme inhibitor (e.g., perindopril and ramipril), acetylcholine agonist (e.g., pramiracetam), protein systhesis antagonist (e.g., procysteine), phosphodiesterase inhibitor (e.g., propentofylline), opioid kappa receptor agonist (e.g., 10H-phenothiazine-2-carboxamine derivatives), complement factor inhibitor (sCRI fragments), somatomedin-1, carnitine acetyltransferase stimulant (e.g., acetylcarnitine), and the like;

T cell inhibitors such as synthetic leucocyte antigen derived peptides, interleukin-1 receptor antagonist, MG/AnergiX, anti-CD3 monoclonal antibodies, anti-CD23 monoclonal antibodies, anti-CD28 antibodies, anti-CD2 monoclonal antibodies, CD4 antagonists, anti-E selectin antibodies, MHC inhibitors, monogens, mycophenolate mofetil, LRA-1 inhibitors, selectin inhibitors, and the like;

antimigraine agents, such as MK-462, 324C91, Phytomedicine, (S)-fluoxetine, calcium channel antagonists (e.g., nimodipine/Nimotop, flunarizine, dotarizine/FI-6026, iomerizine HCL/KB-2796, CPC-304, and CPC-317), α-dihydroergocryptine, 5-HT1 agonists, (e.g., Sumatriptan/Imitrex, Imigran, GR-85548, 311C, and GR-127607), 5-HT1D agonists, 5-HT1A antagonists, 5-HT1B antagonists (e.g., CP-93129), 5-HT1D antagonists (e.g., 1H-indole-5-ethanesulfonamide derivatvies and 1H-indole-5-methanesulfonamide), 5-HT1D receptor cloned (e.g., 5-HT1D agents),

2-thiophenecarboxamide, 3-piperidinamine, diclofenac potassium, dihydroergotamine (e.g., DHE 45®), ergotamine tartrate, dolasetron mesilate, dotarizine, flupirtine, histamine-H3 receptor agonist, indobufen, 1-azulenesulfonic acid derivatives, cholinesterase inhibitors, (e.g., S-9977), bradykinin antagonists, nitric oxide reductase inhibitors (e.g., BN-52296), nitric oxide receptor antagonists, substance P antagonists (e.g., Capsaicin/Nasocap), endopeptidase inhibitors (e.g., neutral endopeptidase, cloned), piperazine derivatives, neurokinin 1 antagonists, metergoline, dopamine D2 antagonist (e.g., metoclopramide + lysine acetyl), enkephalinase inhibitors (e.g., neutral endopeptidase), 5-HT2 antagonists (e.g., LY-053857), 5-HT3 antagonists (e.g., Dolasetron mesilate/MDL-73147, and 4H-carbazol-4-one derivatives), tenosal, tolfenamic acid, cyclooxygenase inhibitors (e.g., carbasalate/carbaspirin calcium, and tenosal/MR-Y134), alpha adrenoreceptor antagonists (e.g., arotinolol, and dihydroergocryptine), opioid agonists (e.g., flupirtine/D-9998), beta adrenergic antagonists (e.g., propranolol), valproate semisodium, propanolol hydrochloride, isometheptene mucate, dichloralphenazone, and the like;

antiarthritic agents, such as anti-CD4 monoclonal antibodies, phospholipase A1 inhibitor, loteprednol, tobramycin, combinations of loteprednol and tobramycin, salnacedin, amiprilose, anakinra, anergiX, anti-B7 antibody, anti-CD3H, anti-gp39, anti-MHC MAbs, antirheumatic peptides, anti-Tac(Fv)-PE40, AP-1 inhibitors, AR-324, purine nucleotide phosphorylase inhibitors (e.g., BCX-5), bindarit,

CD2 antagonist (e.g., BTI-322), campath-1H, CD4 antagonist (e.g., CE9.1 and SB-210396), tumor necrosis factor antagonist (e.g., p80 TNFR, rhTNFbp, peptide T, CenTNF, thalidomide, CDP-571 and TBP-1), cobra venom factor, interleukin 1a agonist (e.g., cytogenin), interleukin 2 receptor antagonist (e.g., dacliximab), ICAM 1 antagonist (e.g., enlimomab), interleukin 1 beta converting enzyme inhibitors (e.g., ICE-inhibitors), interferons (e.g., thymocartin), interleukin-10, interleukin-13, interleukin 1 antagonist (e.g., SR-31747 and TJ-114), interleukin-2 antagonist (e.g., sirolimus), phospholipase C inhibitor, neurokinin 1 antagonist (e.g., L-733060), laflunimus, leflunomide, leucotriene antagonists, levamisole, LFA3TIP, macrocyclic lactone, MHC class II inhibitors, mizoribine, mycophenolate mofetil, NfkB inhibitors, oncolysin CD6, peldesine, pidotimod, PKC-RACK inhibitors, PNP inhibitors, reumacon, CD28 antagonist, roquinimex, RWJ-50271, subreum, T7 vector, tacrolimus, VLA antagonist (e.g., TBC-772), transforming growth factor beta agonist, methionine synthase inhibitors (e.g., vitamin B12 antagonist), adenosine A2 receptor agonist (e.g., YT-146), CD5 antagonist (e.g., zolimomab), 5-lipoxygenase inhibitor (e.g., zileuton, tenidap, and ABT-761), cyclooxygenase inhibitor (e.g., tenoxicam, talmetacin, piroxicam, piroxicam cinnamate, oxaprozin, NXTHIO, ML-3000, mofezolac, nabumetone, flurbiprofen, aceclofenac, diclofenac, and dexibuprofen), metalloproteinase inhibitor (e.g., XR-168, TNF convertase inhibitors, GI-155704A, AG-3340 and BB-2983), nitric oxide synthase inhbitors (i.e, ARL-16556), phospholipase A2 inhibitor (e.g., ARL-67974), selectin antagonist (e.g., CAM inhibitors),

leucotriene B4 antagonist (e.g., CGS-25019C), collagenase inhibitor (e.g., GR-129574A), cyclooxygenase 2 inhibitor (e.g., meloxicam), thromboxane synthase inhibitor (e.g., curcumin), cysteine protease inhibitor (e.g., GR-373), metalloproteinase inhibitor (D-5410), lipocortins synthesis agonist (e.g., rimexolone, predonisolone 21-farnesylate, HYC-141, and deflazacort), chelating agent (diacerein), elastase inhibitors, DNA directed RNA polymerase inhibitor (e.g., estrogens), oxygen radical formation antagonist (e.g., glucosamine sulfate), thrombin inhibitors (e.g., GS-522), collagen inhibitors (e.g., halofuguinone), hyaluronic acid agonist (e.g., NRD-101, hylan, Dispasan, and Hyalart), nitric oxide antagonists (e.g., hydroxocobalamin), stromelysin inhibitors (e.g., L-758354), prostaglandin E1 agonist (e.g., misoprostol, and misoprostol+diclofenac), dihydrofolate reductase inhibitor (e.g., trimetrexate, and MX-68), opioid antagonist (e.g., nalmefene), corticotropin releasing factor antagonist (e.g., NBI-103, and NBI-104), proteolytic enzyme inhibitor (e.g., protease nexin-1, and NCY-2010), bradykinin antagonist (e.g., tachykinin antagonists, and NPC-17731), growth hormone antagonist (e.g., octreotide), phosphodiesterase IV inhibitor (e.g., PDEIV inhibitors), gelatinase inhibitor (e.g., REGA-3G12), free radical scavengers (e.g., SIDR-1026), prostaglandin synthase inhibitors (e.g., sulfasalazine), phenylbutazone, penicillamine, salsalate, azathioprine, indomethacin, meclofenamate sodium, gold sodium thiomalate, ketoprofen, auranofin; aurothioglucose, tolmetin sodium, and the like;

antigout agents (e.g., colchicine, allopurinol, and the like);

anticoagulants (e.g., heparin, heparin sodium, warfarin sodium, and the like);

thrombolytic agents (e.g., urokinase, streptokinase, altoplase, and the like);

antifibrinolytic agents (e.g., aminocaproic acid);

hemorheologic agents (e.g., pentoxifylline);

antiplatelet agents (e.g., aspirin, empirin, ascriptin, and the like);

anticonvulsants (e.g., valproic acid, divalproate sodium, phenytoin, phenytoin sodium, clonazepam, primidone, phenobarbitol, phenobarbitol sodium, carbamazepine, amobarbital sodium, methsuximide, metharbital, mephobarbital, mephenytoin, phensuximide, paramethadione, ethotoin, phenacemide, secobarbitol sodium, clorazepate dipotassium, trimethadione, and the like);

agents useful for calcium regulation (e.g., calcitonin, parathyroid hormone, and the like);

antibacterial agents (e.g., amikacin sulfate, aztreonam, chloramphenicol, chloramphenicol palmitate, chloramphenicol sodium succinate, ciprofloxacin hydrochloride, clindamycin hydrochloride, clindamycin palmitate, clindamycin phosphate, metronidazole, metronidazole hydrochloride, gentamicin sulfate, lincomycin hydrochloride, tobramycin sulfate, vancomycin hydrochloride, polymyxin B sulfate, colistimethate sodium, colistin sulfate, and the like);

antifungal agents (e.g., griseofulvin, keloconazole, and the like);

antiviral agents (e.g., interferon gamma, zidovudine, amantadine hydrochloride, ribavirin, acyclovir, and the like);

antimicrobials (e.g., cephalosporins (e.g., cefazolin sodium, cephradine, cefaclor, cephapirin sodium,

ceftizoxime sodium, cefoperazone sodium, cefotetan disodium, cefutoxime azotil, cefotaxime sodium, cefadroxil monohydrate, ceftazidime, cephalexin, cephalothin sodium, cephalexin hydrochloride monohydrate, cefamandole nafate, cefoxitin sodium, cefonicid sodium, ceforanide, ceftriaxone sodium, ceftazidime, cefadroxil, cephradine, cefuroxime sodium, and the like), penicillins (e.g., ampicillin, amoxicillin, penicillin G benzathine, cyclacillin, ampicillin sodium, penicillin G potassium, penicillin V potassium, piperacillin sodium, oxacillin sodium, bacampicillin hydrochloride, cloxacillin sodium, ticarcillin disodium, azlocillin sodium, carbenicillin indanyl sodium, penicillin G potassium, penicillin G procaine, methicillin sodium, nafcillin sodium, and the like), erythromycins (e.g., erythromycin ethylsuccinate, erythromycin, erythromycin estolate, erythromycin lactobionate, erythromycin siearate, erythromycin ethylsuccinate, and the like), tetracyclines (e.g., tetracycline hydrochloride, doxycycline hyclate, minocycline hydrochloride, and the like), and the like);

antioxidants (e.g., N-acetylcsysteine, Vitamin A, Vitamin C, Vitamin E, ß-carotene, EUK-8, flavonoids, glutathione, α-lipoic acid, melatonin, retinols, and the like);

anti-infectives (e.g., miconazole, vidarabine, inosine, pranobex, vidarabine, inosine prabonex, cefpimizole sodium), fradiomycin, and the like);

bronchodialators (e.g., sympathomimetics (e.g., epinephrine hydrochloride, metaproterenol sulfate, terbutaline sulfate, isoetharine, isoetharine mesylate, isoetharine hydrochloride, albuterol sulfate, albuterol, bitolterol, mesylate isoproterenol hydrochloride, terbutaline sulfate,

epinephrine bitartrate, metaproterenol sulfate, epinephrine, epinephrine bitartrate), anticholinergic agents (e.g., ipratropium bromide), xanthines (e.g., aminophylline, dyphylline, metaproterenol sulfate, aminophylline), mast cell stabilizers (e.g., cromolyn sodium), inhalant corticosteroids (e.g., flurisolidebeclomethasone dipropionate, beclomethasone dipropionate monohydrate), salbutamol, beclomethasone dipropionate (BDP), ipratropium bromide, budesonide, ketotifen, salmeterol, xinafoate, terbutaline sulfate, triamcinolone, theophylline, nedocromil sodium, metaproterenol sulfate, albuterol, flunisolide, and the like);

hormones (e.g., androgens (e.g., danazol, testosterone cypionate, fluoxymesterone, ethyltostosterone, testosterone enanihate, methyltestosterone, fluoxymesterone, testosterone cypionate), estrogens (e.g., estradiol, estropipate, conjugated estrogens), progestins (e.g., methoxyprogesterone acetate, norethindrone acetate), corticosteroids (e.g., triamcinolone, betamethasone, betamethasone sodium phosphate, dexamethasone, dexamethasone sodium phosphate, dexamethasone acetate, prednisone, methylprednisolone acetate suspension, triamcinolone acetonide, methylprednisolone, prednisolone sodium phosphate methylprednisolone sodium succinate, hydrocortisone sodium succinate, methylprednisolone sodium succinate, triamcinolone hexacatonide, hydrocortisone, hydrocortisone cypionate, prednisolone, fluorocortisone acetate, paramethasone acetate, prednisolone tebulate, prednisolone acetate, prednisolone sodium phosphate, hydrocortisone sodium succinate, and the like), thyroid hormones

(e.g., levothyroxine sodium) and the like), and the like;

hypoglycemic agents (e.g., human insulin, purified beef insulin, purified pork insulin, glyburide, chlorpropamide, glipizide, tolbutamide, tolazamide, and the like);

hypolipidemic agents (e.g., clofibrate, dextrothyroxine sodium, probucol, lovastatin, niacin, and the like);

proteins (e.g., DNase, alginase, superoxide dismutase, lipase, and the like);

nucleic acids (e.g., sense or anti-sense nucleic acids encoding any therapeutically active protein, including the proteins described herein, and the like);

agents useful for erythropoiesis stimulation (e.g., erythropoietin);

antiulcer/antireflux agents (e.g., famotidine, cimetidine, ranitidine hydrochloride, and the like);

antinauseants/antiemetics (e.g., meclizine hydrochloride, nabilone, prochlorperazine, dimenhydrinate, promethazine hydrochloride, thiethylperazine, scopolamine, and the like);

septic shock agents, such as angiogenesis inhibitors (OLX-514), bradykinin antagonists (e.g., CP-0502, and NPC-17731), complement factor inhibitors (e.g., C3 convertase inhibitor), C5a release inhibitors (e.g., CAB-2.1), dopamine agonists (e.g., dopexamine), elastase inhibitors (e.g., ONO-5046), E selectin antagonists (e.g., CY-1787), farnesyltransferase inhibitors (RBE limonene), immunostimulants (e.g., CGP-19835A, lipid A vaccine, edobacomab, nebacumab, StaphGAM, and diabodies), immunosuppressants (e.g., CytoTAB, and transcyclopentanyl purine analogues), interleukin 1 antagonists (e.g., interleukin 1 receptors), interleukin 1 receptor

antagonists (e.g., anakinra), interleukin 1b antagonists (e.g., interleukin-1ß), interleukin 1beta converting enzyme inhibitors (e.g., ICE-inhibitors), interleukin 8 antagonists (e.g., IL-8 receptor), interleukin 13 agonists (e.g., intereleukin-13), ITF-1697, lipase clearing factor inhibitors (e.g., SC-59735), membrane permeability enhancers (e.g., Bactericidal Permeability Increasing protein/BPI), nitric oxide antagonists (e.g., hydroxocobalamin), nitric oxide synthase inhibitors (e.g., L-NMMA, and α-methyl-N-delta-iminoethyl-ornithine), P2 receptor stimulants (e.g., ATP analogues), phosphatidic acid synthesis antagonists (e.g., lisofylline), phospholipase A2 inhibitors (e.g., S-448, acylpyrrole-alkanoic acid derivatives, and indoleacetic acid derivatives), platelet activating factor antagonists (e.g., ABT-299, TCV-309, SM-12502, (2RS,4R)-3-(2-(3-pyridinyl)-thiazolidin-4-oyl)indoles, UR-12670, and E-5880), prostacyclin agonists (e.g., taprostene), prostaglandin E1 agonists (e.g., TLC C-53), protein kinase inhibitors (e.g., SB-203580), protein kinase C inhibitors, protein synthesis antagonists (e.g., procysteine), proteolytic enzyme inhibitors (e.g., nafamostat), SDZ-PMX-622, selectin antagonists (e.g., sulfated glycolipid cell adhesion inhibitors), thrombin inhibitors (e.g., GS-522), TNF receptor-Ig, tumor necrosis factor antagonists (e.g., anti-TNF MAbs, MAK-195F, TBP-I, Yeda, rhTNFbp, and CDP-571), tumor necrosis factor alpha antagonists (e.g., E-5531), and the like;

multiple sclerosis agents, such as 4-aminopyridine, 15±deoxyspergualin, ACTH, amantadine, antibody adjuvants (e.g., poly-ICLC, and poly-IC+poly-L-lysine+carboxymethylcellulose),

anti-cytokine MAb (CDP-835), anti-inflammatory (e.g., CY-1787, and CY-1503), anti-selectin MAb (e.g., CY-1787), anti-TCR MAb (e.g., NBI-114, NBI-115, and NBI-116), bacloten, bethanechol chloride, carbamazepine, carbohydrate drugs (e.g., CY-1503), clonazepam, CNS and immune system function modulators (e.g., NBI-106, and NBI-107), cyclophosphamide, cyclosporine A, cytokines (e.g., IFN-α, alfaferone, IFN-ß 1b, betaseron, TGF-ß2, PEG-TGF-ß2, betakine, IFN-ß/Rebif, frone, interferon-ß, and IFN-ß), CD4+T cell inhibitors (e.g., AnergiX), CD28 antagonists (e.g., B7-1, B7-2, and CD28), directcytotoxicity therapies (e.g., benzoporphyrin derivative (BPD)), FK-506, growth factors (e.g., glial growth factor, GGF, nerve growth factors, TGF-ß2, PEG-TGF-ß2, and betakine), humanized MAb (e.g., anti-IFN-γMAb, smart anti-IFN-γMAb, anti-Tac antibody, and smart anti-Tac antibody), humanized anti-CD4 MAb (e.g., anti-CD4 MAb, centara), hydrolase stimulants (e.g., castanospermine), IFN-α, IFN-γ antagonist (e.g., anti-IFN-γ MAb, and smart anti-IFN-γ MAb), IL-2 antagonists (e.g., tacrolimus, FK-506, FR-900506, Fujimycin, Prograf, IL-2 fusion toxin, and DAB_{389}IL-2), IL-4 antagonists (e.g., IL-4 fusion toxin, and DAB_{389}IL-4), immune-mediated neuronal damage inhibitors (e.g., NBI-114, NBI-115, and NBI-116), immunoglobins, immunostimulants (e.g., poly-ICLC, edelfosine, ALP, ET-18-OCH3, ET-18-OME, NSC-24, and poly-IC+poly-L-lysine+carboxymethyl-cellulose), immunosuppressants (e.g., azathioprine, AI-100 animal protein, rDNA human protein AI-101, peptide, AI-102, castanospermine, tacrolimus, FK-506, FR-900506, Fujimycin, Prograf, anti-leukointegrin MAb, Hu23F2G, primatized anti-CD4 antibody, CE9.1, Galaptin

14-1, GL14-1, Lectin-1, recombinant IML-1, linomide, roquinimex, LS-2616, transcyclo-pentanyl purine analogs, MS-6044, spanidin, 15-deoxyspergualin, deoxyspurgiline, gusperimus HCL, NSC-356894, NKT-01, TCR, CD3/Ti, cyclosporine, OL-27-400, SandImmune, Human IL-10, monogens, anti-TCR MAbs, TCAR MAbs, Monogen TM19, Monogen TM27, Monogen TM29, Monogen TM31, peptigen TP12, anti-CD4 MAb, cantara, immunophilins, VX-10367, VX-10393, VX-10428, synthetic basic copolymer of amino acids, copolymer-1, COP-1, T lymphocyte immunofusion (TIF) protein, and cyclophosphamide), integrin antagonists (e.g., anti-integrin (cell adhesion molecule α4ß1 integrin) MAbs, AN-100225, and AN-100226), interferon agonists (e.g., poly-ICLC, and poly-IC+poly-L-lysine+carboxymethyl-cellulose), interferon-ß-1b, isoprinosine, IV methylprednisolone, macrolides (e.g., tacrolimus, FK-506, FR-900506, Fujimycin, and Prograf), MAO B inhibitors (e.g., selegiline, and Parkinyl), methotrexate, mitoxantrone, muscle relaxants (e.g., RGH-5002), muscarinic antagonists (e.g., RGH-5002), neurosteroids (e.g., NBI-106, and NBI-107), octapeptides (e.g., peptide T), oxybutinin chloride, oxygen free radical antagonists (e.g., tetrandrine, biobenzylisoquinoline alkaloid), peptide agonists (e.g., peptide T), phenoxybenzamine, phospholipase C inhibitors (e.g., edelfosine, ALP, ET-18-OCH3, ET-18-OME, NSC-24), photodynamic therapies (e.g., benzoporphyrin derivative (BPD)), plasmapheresis, platelet activating factor antagonists (e.g., ginkgolide B, and BN-52021), potassium channel antagonists (e.g., aminodiaquine, and EL-970), propranolol, prostaglandin synthase inhibitors (e.g.,

sulfasalazine, salazosulfa-pyridine, PJ-306, SI-88, azulfidine, salazopyrin), protease antagonists (e.g., ginkgolide B, and BN-52021), recombinant soluble IL-1 receptors, spergualin analogs (e.g., spanidin, 15-deoxyspergualin, deoxyspurgiline, gusperimus HCl, NSC-356894, NKT-01), TCR peptide decoys (e.g., NBI-114, NBI-115, and NBI-116), TCR peptidomimetic decoys (e.g., NBI-114, NBI-115, and NBI-116), TCR peptide vaccines (e.g., AI-208 (Vß6.2/6.5 phenotype)), selectin antagonists (e.g., lectin-1, and recombinant IML-1), soluble TNF receptor I, TCARs (e.g., TCR, CD3/Ti, and peptigen TP12), TNF antagonists (e.g., thalidomide, and TNF inhibitors), tricyclic antidepressants, and the like;

organ transplantation agents, such as anti-CD25 MAbs, anti-Tac antibodies, anti-TNF MAb (e.g., CDP571), apoptosin, azathioprines (e.g., imuran), BCX-34, CA3, CD28, complement inhibiting factors (e.g., CD59), CTLA4Ig, cyclosporines (e.g., CsA), FK-506/rapamycin binding proteins (FKBP), glucocorticoids, humanized version of OKT3 (e.g., huOKT3-185), mycophenolate mofetil, hydroorotate dehydrogenase inhibitors (e.g., Brequinar), orthoclone OKT3 (e.g., IgG2a anti-T cell murine monoclonal antibody, and muromonab-CD3), rapamycins (e.g., AY-22989), and streptomyces isolates (e.g., FR-900520, and FR-900523), and the like;

systemic lupus erythematosus (SLE) agents, such as androgen-derived steriods (e.g., Org-4094), anti-CD4 humanized antibodies, anti-DNA/V-88, anti-idiotypic murine MAb (e.g., anti-idiotypic antibody to 3E10/MAb1C7), CD2 antagonists (e.g., CD2), complement inhibitors (e.g., recombinant MCP-based complement inhibitors), cyclosporines

(e.g., Sandimmune, cyclosporine analog, OG-37325, cyclosporin-G, and NVal-CyA), cytokines (e.g., IL-4 fusion toxin), cytokine receptor antagonists (e.g., immunomodulatory cytokines), E-selectin antagonists (e.g., anti-ELAM, and CY-1787), FK506/tacrolimus (e.g., Prograf), hypercalcemic agents (e.g., KH-1060), IFN-γ antagonists (e.g., anti-IFN-γ MAb, and smart anti-IFN-γ MAb), IL-1ß converting enzyme inhibitors (ICE), IL-2 produced by E. coli (e.g., celmoleukin, IL-2, TGP-3, and Celeuk), immunoglobulins (e.g., anti-ELAM, CY-1788, and humanized CY-1787), immunostimulants (e.g., thymotrinan, RGH-0205, and TP3), immunosuppressants (e.g., Rapamycin, AY-22989, NSC-226080, NSC-606698, anti-CD4, T-cell inhibitor, anti-tac MAb, smart anti-tac MAb, Migis (membrane immunoglobulin-isotope specific) antibodies, SM-8849, immunophilins, VX-10367, VX-10393, VX-10428, mycophenolate mofetil, ME-MPA, RS-61444, cyclosporine, OL-27-400, Sandimmune, IL-4 fusion toxin, trypanosomal inhibitory factor (TIF), T-cell receptor, CD3/Ti, Org-4094, anti-TBM, CP 17193, Leflunomide/A-77-1726, ELAM-1, AnergiX, Spanidin, 15-deoxyspergualin, deoxyspurgiline, gusperimus hydrochloride, NSC-356894, NKT-01, Roquinimex, LS-2616, linomide, LJP-394, and CD-59 antigen), immunotoxins (e.g., Zolimomab aritox, xmmly-h65-rta, xomazyme-lym/CD5-Plus, OrthoZyme-CD5+, XomaZyme-H65-rta, Xomazyme-CD5 Plus), intravenous immunoglobulins (e.g., IVIG), integrin antagonists (e.g., integrin blockers), Migis™ antibodies, monoclonal antibody therapeutics, murine MAb (e.g., anti-SLE vaccine, and MAb 3E10), primatized anti-CD4 antibodies (e.g., CE9.1), protease inhibitors (e.g., matrix metalloprotease (MMP) inhibitors, and

stromelysin), protein synthesis antagonists (e.g., anti-CD6-bR, anti-T12-bR, and oncolysin CD6), purine nucleoside phosphorylase inhibitors (e.g., BCX-25, and BCX-14), selectin antagonists (e.g., CY1503, and Cylexin), spergualin analogues (e.g., Spanidin, 15-deoxyspergualin, deoxyspurgiline, gusperimus hydrochloride, NSC-356894, and NKT-01), T cell inhibitors (e.g., AnergiX), tumor necrosis factor (TNF) antagonists, and the like;

Alzheimer's disease agents, such as ACh release enhancers (e.g., T-588 (benzothiophene derivative)), acetylcholine release stimulants (e.g., DUP-996 and analogues), AMPA agonists (e.g., AMAlex, and Isoxazole compound series), AMPA GluR agonist (e.g., IDRA-21 [7-chloro-3-methyl-3,4-dihydro-2H-1,2,4-benzothiadiazinine]), AMPA GluR antagonists (e.g., S-18986, and related quinolone derivatives), anticholinesterases (e.g., E-2020), Ca-antagonists (e.g., NS-649, spider venom-derived ICM peptides and analogues, and substituted 2-aminoindanes compound series), combined anticholinesterase and muscarinic AChR antagonists (e.g., PD142676), K-channel blockers (e.g., Trans-R-4-(4-methoxyphenyl-methyl) cyclohexylanine and analogues, and margatoxin-based functional and/or structural analogues), MI muscarinic receptor agonists (e.g., Xanomeline), NMDA antagonists (e.g., certain indole derivatives, and (R-(R^1,S^1))-α-(4-hydroxyphenyl)-beta-methyl-4-(phenylmenthyl)-1-piperidinepropanol and analogues), nicotinic AChR agonists (e.g., ABT-418 [isoxazole, 3-meth-5-(1-meth-2-pyrrolidinyl)]), and the like;

antiparkinson agents (e.g., ethosuximide, and the like);

psoriasis agents, such as 5-LO inhibitors (e.g., Wy-50295, Wy-49232, Lonapalene, RS-43179, MK-886, L-663536,

ETH-615, DUP-654, Zileuton, epocarbazolin-A, and A-64077), 5-LO/CO inhibitors (e.g., BF-397, Tenidap, CP-309, and CP-66248), angiogenesis inhibitors (e.g., platelet factor 4), anticancer antibiotic (e.g., AGM-1470, and TNP-470), anti-inflammatory cytochrome P450 oxidoreductase inhibitors (e.g., DuP-630, and DuP-983), antiproliferative compounds (e.g., Zyn-Linker), arachidonic acid analogues (e.g., CD581, and CD554), arachidonic acid antagonists (e.g., Lonopalene, RS-43179, triamcinolone acetonide with penetration enhancer Azone, betamethasone dipropionate steroid wipe, G-202, Halobetasol propionate, ultravate, Halometasone, C-48401-Ba, and Sicorten), beta-glucan receptor antagonists, betamethasone steroid wipes, calcium metabolic moderators (e.g., Tacalcitol, Bonealfa, TV-02 ointment, Ro-23-6474, KH-1060, Calcipotriol, BMS-181161, BMY-30434, Dovonex, and Divonex), CD4 binding inhibitors (e.g., PIC 060), cell adhesion compounds (e.g., CY-726, VCAM-1, ELAM-1, and ICAM), cell adhesion inhibitors (e.g., selectin inhibitor, GM-1930), cellular aging inhibitors (e.g., Factor X), corticosteroids (e.g., Halobetasol propionate, ultravate, Halometasone, C-48401-Ba, and Sicorten), cyclosporin analogues (e.g., IMM-125), dihydrofolate reductase inhibitors (e.g., G-301, dichlorobenzoprim, methotrexate, and methotrexate in microsponge delivery system), E-selectin inhibitors (e.g., ISIS 4730), endogenous active form of vitamin D_3 (e.g., Calcitriol, and Du- 026325), fibroblast growth factor antagonists (e.g., Saporin mitotoxin, and Steno-Stat), fumagillin analogues (e.g., AGM-1470, and TNP-470), G-proteins and signal transduction compounds (e.g., CPC-A), gel formulations for acne (e.g., nicotinamide, N-547,

and Papulex), growth hormone antagonists (e.g., Octreotide, Sandostatin, Lanreotide, angiopeptin, BIM-23014, and Somatuline), humanized antibodies (e.g., anti-CD4 antibody), hydroorotate dehydrogenase inhibitors (e.g., Brequinar sodium, bipenquinate, and DuP-785), ICAM-1 inhibitors (e.g., ISIS 939), IL-1 and other cytokine inhibitors (e.g., Septanil), IL-1 converting ezyme inhibitors, IL-1 receptor antagonists (e.g., Antril), IL-2 antagonists (e.g., Tacrolimus, Prograf, and FK-506), IL-2 receptor-targeted fusion toxins (DAB389IL-2), IL-8 receptors, immunostimulants (e.g., Thymopentin, and Timunox), immunosuppressants (e.g., XomaZyme-CD5 Plus, cyclosporine, Sandimmune, SR-31747, anti-CD11, 18 MAb, Tacrolimus, Prograf, FK-506, and FK-507), immunosuppressive agents targeting FK506 (e.g., immunophilins, VX-10367, and VX-10428), immunotoxins MAb directed against CD antigen (e.g., XomaZyme-CD5 Plus), leukotriene antagonists (e.g., Sch-40120, Wy-50295, and Wy-49232), leukotriene B4 antagonists (e.g., SC-41930, SC-50605, SC-48928, ONO-4057, LB-457, LY-255283, LY-177455, LY-223982, LY-223980, and LY- 255253), leukotriene synthesis inhibitors (MK-886, and L-663536), lipase clearing factor inhibitors (e.g., 1-docosanol, and lidakol), lipid encapsulated reducing agent (e.g., Dithranol), liposomal gel (e.g., Dithranol), LO inhibitors (e.g., CD581, CD554, Masoprocol, and Actinex), lithium succinate ointments (e.g., lithium salts, and Efalith), LO/CO inhibitors (e.g., P-8892, P-8977, CHX-108, and FPL-62064), membrane integrity agonists (e.g., lithium salts, and Efalith), microtubule inhibitors (e.g., Posophyliotoxin-containing compound, and Psorex),

octapeptide somatostatin analogues (e.g., Lanreotide, angiopeptin, BIM-23014, and Somatuline), oligonucleotides (e.g., ISIS 4730, ISIS 3801, ISIS 1939, and IL-1 inhibitors), peptide agonists (e.g., octapeptide, and peptide T), PKC inhibitors, phospholipase A2 compounds, pospholipase D compounds, photodynamic anticancer agents (e.g., 5-aminolevulinic acid, and 5-ALA), photodynamic therapies (e.g., benzoporphyrin derivative, synthetic chlorins, synthetic porphyrins, and EF-9), photosensitizer (e.g., Porfirmer sodium), PKC inhibitors (e.g., Safingol, and Kynac), platelet activating factor antagonists (e.g., TCV-309), platelet aggregation inhibitors (e.g., CPC-A), prodrug NSAIDs (e.g., G-201), prostaglandin agonist (e.g., eicosapentaenoic acid + gamma-linolenic acid combination, and Efamol Marine), protein inhibitors (e.g., SPC-103600, and SPC-101210), protein kinase C (PKC) inhibitors (e.g., Ro-31-7549, Ro-31-8161, and Ro-31-8220), protein synthesis antagonists (e.g., Calcitriol, Du-026325, LG-1069, LG-1064, AGN-190168, Namirotene, and CBS-211A), purine nucleoside phosphorylase inhibitors (e.g., BCX-34), radical formation agonists (e.g., benzoporphyrin derivative), recombinant antileukoproteinases (e.g., ALP-242), retinoids (e.g., BMY-30123, LG-1069, and LG-1064), retinoid derivatives (e.g., AGN-190168), rapamycin binding proteins (FKBP) (e.g., immunophilins, VX-10367, and VX-10428), second generation monoaromatic retinoids (e.g., Acitretin, and Neotigason), soluble IL-1, IL-4 and IL-7 receptors, somatostatin and somatostatin analogues (e.g., Octreotide, and Sandostatin), steroids, (e.g., AGN-191743), streptomyces anulatus isolates

(e.g., epocarbazolin-A), superoxide dismutase (e.g., EC-SOD-B), thymidylate synthase inhibitors (e.g., AG-85, MPI-5002, 5-FU in biodegradable gel-like matrix, 5-FU and epinephrine in biodegradable gel-like matrix, and AccuSite), topical formulations (e.g., P-0751, and P-0802), transglutaminase inhibitors, tyrphostin EGF receptor kinase blockers (e.g., AG-18, and AG-555), VCAM-1 inhibitors (e.g., ISIS 3801), vitamin D analogues (e.g., Ro-23-6474, KH-1060, Calcipotriol, BMS-181161, BMY-30434, Dovonex, and Divonex), vitamin D_3 analogues (e.g., Tacalcitol, Bonealfa, TV-02 ointment), and vitamin D_3 derivatives (e.g., 1,2-diOH-vitamin D_3), and the like;

diabetes agents, such as ACE inhibitors (e.g., captopril), amylin, amylin agonists and antagonists (e.g., Normylin™, AC137, GC747, AC253, and AC625), autoimmune compounds (e.g., AI-401), capsaicins (e.g., Zostrix-HP), cell regulators (e.g., protein kinase C inhibitors, and Balanol), domperidones (e.g., Motilium®), fluvastatins (e.g., Lescol), FOX 988, fusion toxins (e.g., DAB_{389}IL-2, and DAB_{486}IL-2), gene therapies (e.g., Transkaryotic Therapies), glucagons (e.g., recombinant yeast glucagon), IL-10 compounds, iloprost, immunosuppressives (e.g., tacrolimus, Prograf, and FK-506), proinsulin, insulin and insulin analogs (e.g., AI-401, Nu-Insulin compounds, Humulin, Iletin, Humalog™, LYs-Pro, and Amaryl), insulin-like growth factors (e.g., Chiron/Ciba-Geigy compounds, Fujisawa compounds, and Genetech compounds), insulinotropins (e.g., Pfizer/Scios Nova compounds), nerve growth factors (e.g., Genentech compounds), oral hypoglycemics (e.g., AS-6, glimepiride, Amaryl, CL 316,243, acarbose, miglitol, recombinant yeast

glucagon, GlucaGen™, NovoNorm™, glipizide, insulinotropin, and CI-991/CS-045), platelet-derived growth factors (e.g., Zymo Genetics/Novo Nordisk compounds), sulfonylureas (e.g., tolbutamide, acetohexamide, tolazamide, and chlorpropramide), T cell approaches (e.g., anergize, AnergiX™, Procept compounds, and T cell Sciences compounds), and tolrestats (e.g., Alredase®, and ARI-509), activin, somatostatin, and the like;

stroke agents, such as 5-HT antagonists (e.g., Piperazine derivative), 5-HT reuptake inhibitors (e.g., Milnacipran, and Dalcipran), 5-HT 1A agonists (e.g., SR-57746A, and SR-57746), 5-HT 3 agonists (e.g., SR-57227), 5-HT 4 antagonists, 5-lipoxygenase inhibitors (e.g., low MW dual 5-lipoxygenase and PAF inhibitor CMI-392), ACh agonists (e.g., Pramiracetam, Choline-L-alfoscerate, L-alpha-glycerylphosphoryl-choline, and Delecit), adenosine agonists (e.g., GP-1-4683, ARA-100, and arasine analogs), adenosine A1 receptor agonists (e.g., Azaisotere, 2-chloro-N-[4 (phenylthio)-1-piperidinyl] adenosine, and 2120136), adenosine reuptake inhibitors (e.g., Diphenyloxazole derivatives), adrenergic transmitter re-uptake inhibitors (e.g., Bifemelane, E-0687, MCI-2016, Alnert, and Celeport), aldose reductase inhibitors (e.g., Spiro-3' pyrroline derivatives), alpha antagonists (e.g., Drotaverine acephyllinate, and Depogen), alpha 2 agonists (e.g., SNAP-5083, SNAP-5608, and SNAP-5682), AMPA receptor agonists (e.g., heterocyclic compound SYM-1207, and heterocyclic compound SYM-1252), AMPA receptor antagonists (e.g., LY-293558, and LY-215490), Ancrod/Arvin, aspirin, benzothiazoles (e.g., Lubeluzole, and R87926), benzodiazepine receptor

antagonists (e.g., 3-oxadiazolyl-1,6-naphthyridine derivatives, Tetracyclic imidazodiazepineseries imidazenil, FID-02-023, and Ro-23-1412), blood substitutes, bradykinin antagonists (e.g., CP-0127, Bradycor, and Septicor), C5a release inhibitors (e.g., protein derivative CMI-46000), calcium antagonists (e.g., Lemildipine, NB-818, NPK-1886, Trimetazidine derivative, Iomerizine KP-2796, Diltiazem analog clentiazem maleate, and TA-3090), calcium channel antagonists (e.g., nitrendipine-like compound diperdipine, YS-201, U-92032, Diltiazem derivative, 1058, SM-6586, KP-840, F-0401, D-31-D, Tetrahydronaphthalene derivatives, fasudil, AT-877, H-7, HA-1044, HA-1077, Eril, darodipine, dazodipine, PY-108-068, Plimo, Dihydropy-ridine, AE 0047, GJ-0956, Lacidipine, GR-43659, GR-43659X, GX-1048, S-312-d, S-312, S-830312, Nilvadipine, and FK-235), calpain inhibitors (e.g., AK-275, and CX-275), carnitine palmitoyl-transferase inhibitors, carvedilol, cerebral calcium antagonist vasodilators (e.g., Nimodipine, and Nimotop), cholinesterase inhibitors (e.g., indole and indazole derivatives, and Tacrine analog), complement factor inhibitors (e.g., TK9C, protein derivative TP16, compinact A, compinact C, Factor D inhibitors, and soluble, recombinant MCP-based complement inhibitors), complement inhibitors (e.g., sCRI/BRL-55730, and YM-203), coronary vasodilators (e.g., Nicorandil, RP-46417, SG-75, and Adancor), CPC-111, cytidyl diphosphocholine/citicholines, cytokines (e.g., NBI-117), Dexanabiol, dopamine agonists, EAA receptors, endothelin antagonists (e.g., SB 209670), endothelin receptor antagonists, excitatory amino acid agonists (e.g., acylated

polyamine analogs, and N-(4-hydroxyphenylpropanonyl)-spermine analog), excitatory amino acid antagonists (e.g., Tryptophan, 4,6-disubstituted stroke & kynurenine derivatives, NPC-17742, CPC-701, and CPC-702), glutamate antagonists (e.g., Kainate quisqualate NNC-07-9202, NPC-17742, small molecule CNS-1237, NS-257, NS-072, BW-619C, CGS 19755, Riluzole, PK-26124, and RP 54274), glutamate receptor antagonists (e.g., Araxin compounds, Quinoxaline derivative, YM-90K, and YM-900), glycine antagonists, glycine NMDA agonists (e.g., 3-hydroxy-2,5-dioxo-1H-benz[b]azepines), glycine NMDA associated antagonists (e.g., 5,6-dihydro-1H-pyrrolo [1,2,3-de] quinoxaline-2,3-diones, Strychnine-insensitive glycine binding site of NMDA receptor L-687414, Glystasins, ACEA-2011, ACEA-3031, AC-1021, ACPC, and eliprodil), growth factor antagonists (e.g., non-peptide indolocarbazole neutrophic molecules, and CEP-075), GPIIb/IIIa antagonists (e.g., Peptide C68-22), hemorheological agents (e.g., Drotaverine acephyllinate, and Depogen), heparin, hydroxyl radical formation inhibitors (e.g., homopiperazine derivative K-7259), hypocalcemic agents (e.g., calcitonin peptide, related to hCGRP peptide), hypothermic agents/BMY-20862, ICAM-1 compounds (e.g., Enlimomab), immunosuppressants (e.g., small molecule compounds, and NBI-117), integrin general antagonists (e.g., monoclonal antibody AN-100225, and monoclonal antibody AN-100226), Interleukin-1 antagonists (e.g., cyclic nitrones), iron-dependent lipid peroxidation inhibitors (e.g., 2-(amino-methyl) chromans), lactic acid accumulation/inhibitors (e.g., small molecule CPC-211), Leukotriene B4 antagonists (e.g.,

Ebselen, DR-3305, PZ-25, PZ-51, RP 60931, and RP 61605), lipid peroxidase inhibitors (e.g., Idebenone, and Avan), low molecular weight small molecules, methyltransferase stimulants (e.g., 4-methyl benzenesulfonate, ademetionine sulfate tosilate, FO-156, and Ceritan), monoamine oxidase B inhibitors (e.g., MD-280040, MD-200243, MD-280080, Lazabemide, and Ro-19-6327), MS-153, MS-424, /Na^+/H^+ Na^+/Li^+ exchange inhibitors (e.g., Pyrazine derivatives), nadroparin (e.g., Fraxiparin), nafronyl/naftidrofuryl (e.g., Praxilene), nerve growth factor agonists (e.g., small molecule compounds, CNTF, BDNF, 2.5S NGF, monosialoganglioside GM1, and Sigen/Sygen), neuronal calcium channel blockers (e.g., CPC-304, and CPC-317), neuronal differentiation compounds (e.g., F-spondin), neuropeptide agonists (e.g., Neurotrophic Peptide Trofexin), neutrophil inhibitory factors (e.g., small molecule compounds), nitric oxide agonists (e.g., hydroxy derivative N-3393, hydroxy derivative N-3398, nicorandil, and Therapicon), nitric oxide antagonists, NMDA antagonists (e.g., Spiroisoindoles/dizocilpine derivatives, Oxindole compound, CP-112116, LY-104658, LY-235959, FR-115427, Sialic acid derivative, N-palmitoyl-Betaethylglycoside neuraminic acid, ND-37, Ro-01-6794, 706, Dextrorphan, Ifenprodil analogue eliprodil, SL-82.0715, Lipophilic molecules, HU-211, Remacemide, 934-423, 12495, 12859, 12942AA, Selfotel, CGS-19755, SDZ-EAA-494, CGP-40116, CGP-37849, CGP-39551, and CGP-43487), NMDA antagonist-partial agonists (e.g., Conantokin G peptide SYM-1010), NMDA channel blockers (e.g., Aptiganel, CERESTAT, and CNS 1102), NMDA receptor antagonists, NMDA receptor subtypes (e.g., Kainate quisqua-late

NNC-07-9202), non-competitive NMDA antagonists (e.g., FPL-15896), non-ionic copolymer RheothRx, nootropic/acetylcholine agonists (e.g., Oxiracetam, CT-848, and Neuractiv), norepinephrine inhibitors (e.g., Midalci-pran), N-type calcium channel antagonists (e.g., NS-626, and NS-638), opioid antagonists (e.g., Nalmefene, nalmetrene, JF-1, ORF-11676, Cervene, and Incystene), opioid kappa receptor agonists (e.g., acrylacetamide enadoline, and CI-997), organoselenims (e.g., Ebselen, DR-3305, PZ-25, PZ-51, RP 60931, and RP 61605), oxygen scavengers (e.g., Tirilazad mesylate, Lazaroids, and Freedox), PA2 inhibitors (e.g., phospholipase A2 inhibitor), PAF antagonists (e.g., nupafant, and BB-2113), partial glycine NMDA agonists (e.g., ACPC), peptide/ GPIIb/IIIa antagonists (e.g., Integrelin), peptidic neuron-specific calcium channel antagonists (e.g., SNX-111), phosphodiesterase inhibitors (e.g., Xanthine derivatives, propentofylline, Hoe-285, and Hextol), phospholipase A2 inhibitors (e.g., small organic molecule CEP-217), plasminogen activators (e.g., r-ProUK (recombinant pro-urokinase), platelet-activating factor antagonists (e.g., UK-74505), platelet adhesion inhibitors (e.g., Peptide), platelet aggregation antagonists (e.g., cilostazol, peptide agents, GPHb-IIIA inhibitor, and TP-9201), platelet aggregation inhibitors (e.g., Diaminoalkanioic acid derivatives), potassium channel agonists (e.g., Nicorandil, RP-46417, SG-75, and Adancor), prolyl endopeptidase (PEP) inhibitors (e.g., JTP-4819), protein kinase C inhibitors (e.g., monosialoganglioside derivative Liga-20), proteolytic enzyme inhibitors (e.g., Protease nexin-1, Incyte, PN-1, PN-2, Nafamostat, FUT-175,

Duthan, and Futhan), pyrimidine derivatives, Quinolizine derivatives (e.g., KF-17329, and KF-19863), radical formation antagonists (e.g., EPC-K1), recombinant tissue plasminogen activators (e.g., alteplase, and Activase), Schwann cell derived molecules/promoters, sigma antagonists (e.g., Sigma ligand), sigma receptor antagonists (e.g., tetrahyropyridinyl-isoxazolines and isoxazoles PD-144418), sodium/calcium channel modulators (e.g., Lifarizine, and RS-87476), sodium channel antagonists, streptokinase (e.g., Streptase), substituted guanadine (e.g., small molecule CNS-1237), superoxide dismutase stimulants (e.g., PEG conjugated enzyme superoxide dismutase/Dismutec, and PEG-SOD), thrombin inhibitors, (e.g., non-peptide), thromboxane synthase inhibitors (e.g., Linotroban, and HN-11500), thyrotropin-releasing hormone agonists (e.g., TRH agonists, Protirelin analogthymoliberin, and RX-77368,), ticlopidine (e.g., Ticlid), TJ-8007, TRH agonists (e.g., Thyrotropin releasing hormones, and JTP-2942), trilazard, urokinase (e.g., Abbokinase), w-conopeptide (e.g., SNX-111), and warfarin (e.g., Coumadin), and the like;

agents useful for the treatment of carcinomas (e.g., adriamycin, taxol, interleukin-1, interleukin-2 (especially useful for treatment of renal carcinoma), and the like, as well as leuprolide acetate, LHRH analogs (such as nafarelin acetate), and the like, which are especially useful for the treatment of prostatic carcinoma),

agents useful for the treatment of endometriosis (e.g., LHRH analogs),

agents useful for the treatment of uterine contraction (e.g., oxytocin),

agents useful for the treatment of diuresis (e.g., vasopressin),

agents useful for the treatment of cystic fibrosis (e.g., Dnase (i.e., deoxyribonuclease), SLPI, and the like),

agents useful for the treatment of neutropenia (e.g., GCSF),

agents useful for the treatment of lung cancer (e.g., beta 1-interferon),

agents useful for the treatment of respiratory disorders (e.g., superoxide dismutase),

agents useful for the treatment of ischemia/reperfusion injury (e.g., selectin inhibitors, Irf1, and the like);

nitric oxide synthase inhibitors (e.g., N^4-methyl-L-arginine, aminoguanidine, N^6-(iminoethyl)-L-ornithine, thiocitrulline and other citrulline derivatives, N^4-nitro-L-arginine, N^4-nitro-L-arginine methyl ester, N^4-amino-L-arginine, and other arginine derivatives, isothiourea and its derivatives, and the like,

as well as a variety of other agents, such as acyclovir, alendronate sodium, amlodipine, ampicillin, azelaic acid, azithromycin, beclomethasone, betamethasone, bicalutamide, buspirone, carisoprodol, carvedilol, cefaclor, cefadroxil, cefixime, cefprozil, ceftibuten, cefuroxime axetil, cephalexin, cetirizine hydrochloride, cimetidine, ciprofloxacin, cisapride, clarithromycin, clavulanate, clonazepam, clotrimazole, codeine, conjugated estrogens, cyclobenzaprine, desogestrel, dexrazoxane, diazepam, dicyclomine HCl, digoxin, diltiazem, dirithromycin, doxazosin, doxycycline, enalapril, erythromycin, erythromycin base, erythromycin stearate, estradiol, ethinyl estradiol, ethynodiol diacetate, etodolac, famotidine, fluconazole, fluoxetine, fluvastatin, furosemide, gemfibrozil, glipizide, glyburide, guaifenesin,

hydrochlorothiazide, hydrocodone, hydrocortisone, ibuprofen, ibutilide fumarate, indapamide, insulin, ipratropium bromide, ketoconazole, ketoprofen, ketorolac tromethamine, lamivudine, lansoprazole, levonorgestrel, levothyroxine, lisinopril, loracarbef, loratidine, lorazepam, losartan potassium, lovastatin, medroxyprogestrone, methylphenidate, methylprednisolone, metoprolol, metoprolol tartrate, moexipril hydrochloride, mometasone furoate, mupirocin, mycophenolate mofetil, nabumetone, nalmefene hydrochloride, naproxen, neomycin, nifedipine, nisoldipine, nitrofurantoin, nizatidine, norethindrone, norgestrel, nortriptyline, ofloxacin, omeprazole, oxaprozin, oxycodone, paroxetine, penicillin, pentoxifylline, phenylpropanolamine, phenytoin, polymyxin, porfimer sodium, potassium chloride, pravastatin, prednisone, promethazine, propoxyphene, pseudoephedrine, quinapril, ramipril, ranitidine, riluzole, salmeterol, saquinavir mesylate, sertraline, sevoflurane, simvastatin, sucralfate, sulfamethoxasole, sumatriptan, temazepam, terazosin, terconazole, terfenadine, tetracycline, theophylline, timolol, tramadol, tramadol hydrochloride, tretinoin, triamcinolone acetonide, triamterene, trimethoprim, valproic acid, venlafaxine, verapamil, wafarin, zolpidem, and the like.

In accordance with yet another embodiment of the present invention, there are provided methods for reducing the side effects induced by administration of pharmacologically active agent(s) to a subject, said method comprising administering said pharmacologically active agent as part of a therapeutic consisting essentially of said pharmacologically active agent and carbon disulfide in a pharmaceutically acceptable carrier. Alternatively, the carbon disulfide can be delivered in protected form as a physiologically compatible compound which is readily hydrolyzable under selected physiological conditions to release carbon disulfide (e.g., a dithiocarbamate).

In accordance with still another embodiment of the present invention, there are provided methods for enhancing the effectiveness of pharmacologically active agent(s), said method comprising administering said pharmacologically active agent as part of a therapeutic consisting essentially of said pharmacologically active agent and carbon disulfide in a pharmaceutically acceptable carrier. Alternatively, the carbon disulfide can be delivered as a physiologically compatible compound which is readily hydrolyzable under selected physiological conditions to release carbon disulfide.

Those of skill in the art recognize that the therapeutic described herein can be delivered in a variety of ways, such as, for example, orally, intravenously, subcutaneously, parenterally, rectally, by inhalation, and the like.

Depending on the mode of delivery employed, the therapeutic contemplated for use herein can be delivered in a variety of pharmaceutically acceptable forms. For example, the therapeutic can be delivered in the form of a solid, solution, emulsion, dispersion, micelle, liposome, and the like.

Thus, in accordance with still another embodiment of the present invention, there are provided physiologically active composition(s) consisting essentially of a physiologically compatible compound which is readily hydrolyzable under selected physiological conditions to release carbon disulfide in a suitable vehicle rendering said compound(s) amenable to oral delivery, transdermal delivery, intravenous delivery, intramuscular delivery, topical delivery, nasal delivery, and the like.

Pharmaceutical compositions of the present invention can be used in the form of a solid, a solution, an emulsion, a dispersion, a micelle, a liposome, and the like, wherein the resulting composition contains one or more of the compounds of the present invention, as an active ingredient, in admixture with an organic or inorganic carrier or excipient suitable for enteral or parenteral applications. The active ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, solutions, emulsions, suspensions, and any other form suitable for use. The carriers which can be used include glucose, lactose, gum acacia, gelatin, mannitol, starch paste, magnesium trisilicate, talc, corn starch, keratin, colloidal silica, potato starch, urea, medium chain length triglycerides, dextrans, and other carriers suitable for use in manufacturing preparations, in solid, semisolid, or liquid form. In addition auxiliary, stabilizing, thickening and coloring agents and perfumes may be used. The active compound(s) is(are) included in the pharmaceutical composition in an amount sufficient to produce the desired effect upon the process or disease condition.

Pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of a sweetening agent such as sucrose, lactose, or saccharin, flavoring agents such as peppermint, oil of wintergreen or cherry, coloring agents and preserving agents in order to provide pharmaceutically elegant and

palatable preparations. Tablets containing the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients may also be manufactured by known methods. The excipients used may be, for example, (1) inert diluents such as calcium carbonate, lactose, calcium phosphate or sodium phosphate; (2) granulating and disintegrating agents such as corn starch, potato starch or alginic acid; (3) binding agents such as gum tragacanth, corn starch, gelatin or acacia, and (4) lubricating agents such as magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the techniques described in the U.S. Pat. Nos. 4,256,108; 4,160,452; and 4,265,874, to form osmotic therapeutic tablets for controlled release.

In some cases, formulations for oral use may be in the form of hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin. They may also be in the form of soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example, peanut oil, liquid paraffin, or olive oil.

The pharmaceutical compositions may be in the form of a sterile injectable suspension. This suspension may be formulated according to known methods using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Sterile, fixed oils are

conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides, fatty acids (including oleic acid), naturally occurring vegetable oils like sesame oil, coconut oil, peanut oil, cottonseed oil, etc., or synthetic fatty vehicles like ethyl oleate or the like. Buffers, preservatives, antioxidants, and the like can be incorporated as required.

Compounds contemplated for use in the practice of the present invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions may be prepared by mixing the drug with a suitable non-irritating excipient, such as cocoa butter, synthetic glyceride esters of polyethylene glycols, which are solid at ordinary temperatures, but liquify and/or dissolve in the rectal cavity to release the drug.

Since individual subjects may present a wide variation in severity of symptoms and each drug has its unique therapeutic characteristics, the precise mode of administration and dosage employed for each subject is left to the discretion of the practitioner.

In general, the dosage of carbon disulfide or physiologically compatible compound which is readily hydrolyzable under selected physiological conditions to release carbon disulfide falls in the range of about 0.01 mmoles/kg body weight of the subject/hour up to about 0.5 mmoles/kg/hr. Typical daily doses, in general, lie within the range of from about 1 μg up to about 100 mg per kg body weight, and, preferably within the range of from 10 μg to 10 mg per kg body weight and can be administered up to four times daily. The daily IV dose lies within the range of from about 1 μg to about 100 mg per kg body weight, and, preferably, within the range of from 10 μg to 10 mg per kg body weight.

The invention will now be described in greater detail by reference to the following non-limiting examples.

Example 1

Carbon disulfide inhibits nuclear factor kappaB in cultured Jurkat T cells

Jurkat T cells are grown in RPMI 1640 medium supplemented with 10% fetal calf serum and penicillin-streptomycin. The cells are treated with 1 or 5 mM carbon disulfide dissolved in DMSO and the controls are treated with the same amount of DMSO alone for one hour. Both groups of cells are then incubated with either 10 ng/ml tumor necrosis factor or 10 ng/ml IL-1 for one hour. Cells are fractionated and nuclear extracts are prepared as described previously (see, for example, Stylianou, E et al., in J. Biol. Chem., 267:15836-15841 (1992)). The protein in this crude nuclear extract is determined using the method of Bradford. The amount of NFκB expressed is determined by Western blotting using anti-NFκB antibodies. The results show that CS_2 at either 1 or 5 mM levels inhibits the amount of NFκB induced either by TNF or IL-1.

Example 2

Acid hydrolysis of N-methyl-D-glucamine dithiocarbamate or L-proline dithiocarbamate

The uv-visible spectrum of N-methyl-D-glucamine dithiocarbamate in phosphate-buffered saline at pH 7.4 is shown in Figure 1A, in which two prominent peaks appear at 258 nm and 286 nm, respectively. Lowering the pH to 4 caused the rapid disappearance of both peaks, indicative of the cleavage of the amide group to release carbon disulfide. Similar results were obtained for L-proline dithiocarbamate.

Example 3

Oral administration of L-proline dithiocarbamate reduces inflammatory lesions in adjuvant-induced arthritic rats

Lewis rats (male, 180-220 g) were injected intradermally into the right hind footpad with M. tuberculosis (5 mg/ml in light mineral oil). The rats were weighed daily and observed for tarsal joint and footpad swelling. A scoring system of 1-6 to estimate the degree of inflammatory lesions on the uninjected footpad was established to estimate the degree of swelling and deformation of the foot resulting from arthritic conditions. On day 7, the rats were separated into two groups, one received L-proline dithiocarbamate in drinking water (5-10 mg/ml, p.o.) and the other received distilled water alone for 14 days. The results in Figure 2 show that oral administration of L-proline dithiocarbamate significantly reduces the swelling in the uninjected footpad compared to the controls.

Example 4

Heterotopic cardiac transplantation in rats

Lewis (Lew) and Wistar-Furth (WF) rat strains were used for this study. Lew and WF rats represent complete genetic disparity at both the major and minor histocompatibility loci. Lew rats underwent either isogeneic (Lew-Lew) or allogeneic (WF-Lew) heterotopic cardiac transplantation to the abdominal aorta and vena cava by standard microvascular surgical techniques. All cardiac transplants were noted to have good initial contractile function. Graft function was monitored by palpation through the abdominal wall twice daily. Allograft rejection was defined by loss of palpable contractile activity and was confirmed by direct inspection at laparatomy.

Stable end products of nitric oxide generation, plasma nitrite and nitrate were assayed by chemiluminescence on posttransplant day 5. Activity of myocardial nuclear factor kappa B (NFκB), a rapid response transcription factor, was measured on posttransplant day 4 to assess how NFκB-controlled genes are affected by CsA and MGD. NFκB activation was evaluated by electrophoretic mobility shift assay and quantified by phorphorimage analysis. Results are expressed as a percentage of the total amount of radioactivity shifted to the NFκB binding site.

Example 5

Prolongation of allograft survival by combination therapy of N-methyl-D-glucamine dithiocarbamate (MGD) and cyclosporine

Survival of the cardiac allograft in the WF-Lew group averaged about 7 days (see Table 1). (MGD) administration twice daily (400 mg/kg sc) increased allograft survival time by 56%. This form of MGD monotherapy was incapable of preventing allograft rejection. CsA was also tested as a monotherapy but at a dose that would not prevent rejection (2.5 mg/kg im on days 1-7). This low dose CsA regimen increased allograft survival time by approximately 71%. However, the combination therapy of MGD and CsA increased allograft survival by 550% over untreated controls and 280% over CsA monotherapy. Note that with combination therapy, graft survival was extended even though CsA therapy ended on posttransplant day 7.

Table 1

Combination Therapy Increases Mean Survival Time Over MGD or CsA

Monotherapy Group	Treatment	Mean Survival Time
(1) Lew-Lew	None	>100 days
(2) WF-Lew	None	6.9±0.2
(3) WF-Lew	MGD (400 mg/kg sc bid daily until rejection	10.8±0.7*
(4) WF-Lew	CsA (2.5 mg/kg im on days 1-7)	11.8±0.4*
(5) WF-Lew	MGD (400 mg/kg sc bid daily until rejection) + (CsA 2.5 mg/kg im on days 1-7)	45.0±4.7**

*=p<.05 vs Group 2; **=p<.05 vs. Group 2,3,4

Combination therapy reduced nitrate/nitrite production better than monotherapy. The stable end products of nitric oxide generation, plasma nitrite and nitrate were assayed by chemiluminescence on posttransplant day 5. Plasma levels of nitrite/nitrate in WF-Lew were elevated six times over isograft controls (Table 2). Daily treatment with MGD reduced nitrate/nitrite levels 40%. Daily treatment with CsA reduced nitrite/nitrate levels 65%. However, the combination therapy of MGD and low dose CsA resulted in a 79% reduction in measured nitrite/nitrate levels.

Table 2

Combination Therapy Reduces Nitrite/Nitrate Production Better Than MGD or CsA Alone

Group	Treatment	NO_2 and NO_3 (μM)
1) Lew-Lew	None	24.9±2.1
2) WF-Lew	None	159.0±24.6
3) WF-Lew	MGD (400 mg/kg sc bid daily)	93.6±4.9*
4) WF-Lew	CsA (2.5 mg/kg im/day)	56.7±5.0*
5) WF-Lew	MGD (400 mg/kg sc bid daily) + (CsA 2.5 mg/kg im/day)	32.9±3.0**

*=p<.05 vs Group 2; **=p<.05 vs. Group 2,3,4

Combination therapy reduced NFκB expression better than MGD or CsA alone. Allograft rejection stimulates a response that has many inflammation-like characteristics. The transcription factor NFκB, a key initiator of the inflammation cascade, stimulates the expression of many inflammation-related genes including adhesion receptors and iNOS. To evaluate the role of NFκB in allograft rejection and the effect of MGD and CsA on the activation of this transcription factor, NFκB levels were examined in electrophoretic mobility gel shift assays from tissue samples collected on posttransplant day 4.

Table 3 shows that the amount of radioactivity shifted into the NFκB binding site is increased in the presence of the allograft (Group 2). MGD therapy alone reduced NFκB expression by about 50% (Group 3). CsA monotherapy reduced NFκB by 64%. However, the combination of MGD and CsA reduces NFκB by 72% (Group 5).

Table 3

Combination Therapy Reduces NFκB Expression Better Than MGD or CsA Alone

Group	Treatment	NFκB Expression§
1) Lew-Lew	None	2.7±0.3%
2) WF-Lew	None	24.0±3.7%
3) WF-Lew	MGD (400 mg/kg sc bid daily)	12.9±0.8%
4) WF-Lew	CsA (2.5 mg/kg im/day)	9.0±0.5%
5) WF-Lew	MGD (400 mg/kg sc bid daily) + (CsA 2.5 mg/kg im/day)	6.8±0.4%

§Expressed as percent of total radioactivity incorporated into the NFκB binding site

*=p<.05 vs Group 2; **=p<.05 vs. Group 2,3,4

MGD was evaluated for its ability to prevent rejection after long-term, oral administration via the drinking water (Table 4). Monotherapy with low dose CsA until rejection permitted allograft survival for 23 days. However, combination therapy employing low dose of CsA (2.5 mg/kg im/day until rejection) and MGD (5 mg/ml in the drinking water) daily for 100 days resulted in remarkably long term graft survival. Although one graft survived only 16 days after terminating therapy at 100 days, three other animals under MGD and CsA therapy still had surviving grafts 70 days after withdrawing therapy for a total graft survival time of more than 170 days. The mechanism of prolonged survival from long term combination therapy is currently under investigation.

Table 4

MGD (oral) + CsA Combination Therapy Results in Long Term Graft Survival

Group	Treatment	Graft Survival (days)
(1) WF-Lew	CsA (2.5 mg/kg im/day) until rejection	23±2.5
(2) WF-Lew	CsA (2.5 mg/kg im/day) and MGD (5 mg/ml in drinking water) for 100 days	116, >170 (3 animals)

In conclusion, dithiocarbamates such as N-methyl-D-glucamine dithiocarbamate (MGD) or L-proline dithiocarbamate can readily be decomposed to release carbon disulfide in the stomach (Masuda and Nakayama, supra). CS_2 released from these compounds may account for the observed effects in both arthritic model and allograft model in rats mediated via the inhibition of NFκB *in vivo*.

Example 6

Evaluation of the effects of pyrrolidinol dithiocarbamate as a source of CS_2 and ibuprofen on acute gastric mucosal injury

Wistar rats (200-250 grams, male) are fasted overnight but allowed free access to water. Ten rats in each group are given ibuprofen alone or ibuprofen plus dithiocarbamate orally at doses of 10, 20 or 50 mg/kg. The rats are sacrificed five hours later and visible gastric damage is assessed by examining under microscope and histological evaluation.

Example 7

Evaluation of the effects of pyrrolidinol dithiocarbamate as a source of CS_2 and ibuprofen on chronic gastric ulcer

White New Zealand rabbits (male, about 1 kg) are given subcutaneously ibuprofen alone or ibuprofen plus dithiocarbamate at a dose of 30 mg/kg for every 12 hours. The animals are sacrificed on day 4 (after the 7th dose) and the visible ulcers in the stomach are examined and measured with calipers. The tissue samples are fixed in neutral buffered formalin and processed for histological evaluation.

Example 8

Evaluation on the anti-inflammatory effects of pyrrolidinol dithiocarbamate as a source of CS_2 and ibuprofen

Wistar rats (male, 200-250 g) are fasted overnight but allowed to free access to drinking water. Ibuprofen alone or ibuprofen plus dithiocarbamate is given orally at a dose of 1, 10, or 30 mg/kg (6 animals each group). After one hour, the rats are anesthetized and 0.1 ml of lambda carrageenan (0.1% solution) is injected into the right hind foot pad. The volume of the pad is measured by hydroplethysmometry every hour for the next five hours.

Example 9

Evaluation of the effects of pyrrolidinol dithiocarbamate as a source of CS_2 and ibuprofen on prostaglandin synthesis

Wistar rats (male, 200-250 g) are fasted overnight but allowed free access to drinking water. The rats are anesthetized and their backs are shaved. After an incision to the back, a sponge (2.5 x 1 x 0.5 cm) soaked with 2 ml of 0.5% carrageenan is implanted. Five hours later, the rats (6 animals in each group) are given orally either

ibuprofen alone or ibuprofen plus dithiocarbamate at a dose of 30 mg/kg or vehicle control. One hour later, the rat is sacrificed and the sponge is carefully removed. The exudate is recovered from the sponge and the prostaglandin E2 level in the exudate is measured by enzyme-linked immunosorbent assay.

Example 10

Evaluation on the protective effects of L-proline dithiocarbamate as a source of CS_2 against adriamycin-induced cardiotoxicity

Balb/c mice (male, 20-25 g) are fed a standard diet and allowed free access to drinking water. The mice are anesthetized and the telemetry system consisting of implantable transmitters, a telemetry receiver and analog ECG adapter is implanted in the peritoneal cavity of each mouse. After surgery, the mice are allowed to recover for two weeks. The mice are given intravenously either adriamycin alone or adriamycin plus dithiocarbamate at a dose of 4 mg/kg through the tail vein. The treated mice are observed for two weeks. The body weight, ECG and heart rate are recorded daily. At the end of the study, the animals are sacrificed and the hearts are processed for histological evaluation.

While the invention has been described in detail with reference to certain preferred embodiments thereof, it will be understood that modifications and variations are within the spirit and scope of that which is described and claimed.

That which is claimed is:

1. A method for the treatment of an inflammatory condition mediated by nuclear factor kappa-B (NFκB), said method comprising administering to a subject in need thereof an effective amount of a therapeutic consisting essentially of carbon disulfide in a pharmaceutically acceptable carrier.

2. A method according to claim 1 wherein said carbon disulfide is administered in a chemically protected form.

3. A method according to claim 2 wherein said chemically protected form of carbon disulfide is a dithiocarbamate which is readily hydrolyzable under selected physiological conditions.

4. A method according to claim 3 wherein said dithiocarbamate has the structure I, as follows:

$$[R_1R_2N\text{-}C(S)\text{-}S^-]_x\ M^{+1,\ +2,\ +3} \qquad (I)$$

wherein:

each of R_1 and R_2 is independently a C_1 up to C_{18} alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, acyl, substituted acyl, or

R_1 and/or R_2 is a divalent or polyvalent moiety, wherein said divalent or polyvalent moiety serves as the same substituent for two or more dithiocarbamate structures, thereby linking said structures together so as to form a bis(dithiocarbamate) or poly(dithiocarbamate) species,

x is 1 or 2, and

M is a monovalent cation when x is 1, or M is a physiologically compatible divalent or trivalent transition metal cation when x is 2.

5. A method according to claim 4 wherein R_1 and/or R_2 is a divalent moiety selected from the group consisting of alkylene, substituted alkylene, oxyalkylene, substituted oxyalkylene, alkenylene and substituted alkenylene, wherein said divalent moiety serves as the same substituent for two dithiocarbamate structures, thereby linking said structures together so as to form a bis(dithiocarbamate) species.

6. A method according to claim 4 wherein R_1 and/or R_2 is a polyvalent moiety, wherein said polyvalent moiety serves as the same substituent for a plurality of dithiocarbamate structures, thereby linking said structures together so as to form a poly(dithiocarbamate) species.

7. A method according to claim 4 wherein:

each of R_1 and R_2 is independently a C_1 up to C_{12} alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl or substituted alkynyl, wherein the substituents are selected from carboxyl, -C(O)H, oxyacyl, phenol, phenoxy, pyridinyl, pyrrolidinyl, amino, amido, hydroxy, nitro or sulfuryl, and

M = Fe^{+2} or Fe^{+3}.

8. A method according to claim 4 wherein:

R_1 is a C_2 up to C_6 alkyl or substituted alkyl, wherein the substituents are selected from carboxyl, acetyl, pyridinyl, pyrrolidinyl, amino, amido, hydroxy or nitro, and

R_2 is a C_1 up to C_6 alkyl or substituted alkyl, and

M = Fe^{+2}.

9. A method according to claim 4 wherein:

R_1 is a C_2 up to C_4 alkyl or substituted alkyl, wherein the substituents are selected from carboxyl, acetyl, amido or hydroxy, and

R_2 is a C_1 up to C_4 alkyl or substituted alkyl, and

$M = Fe^{+2}$.

10. A method according to claim 1 wherein said carbon disulfide in a pharmaceutically acceptable carrier is administered orally.

11. A method according to claim 2 wherein said chemically protected form of carbon disulfide in a pharmaceutically acceptable carrier is administered orally.

12. A method according to claim 1 wherein said carbon disulfide in a pharmaceutically acceptable carrier is administered intravenously, subcutaneously, parenterally, rectally or by inhalation.

13. A method according to claim 1 wherein said inflammatory condition is septic shock, hemorrhagic shock, anaphylactic shock, toxic shock syndrome, ischemia, cerebral ischemia, administration of cytokines, overexpression of cytokines, ulcers, inflammatory bowel disease, diabetes, arthritis, asthma, Alzheimer's disease, Parkinson's disease, multiple sclerosis, cirrhosis, allograft rejection, encephalomyelitis, meningitis, pancreatitis, peritonitis, vasculitis, lymphocytic choriomeningitis, glomerulonephritis, uveitis, ileitis, inflammation, burn, infection, hemodialysis, chronic fatigue syndrome, stroke, cancers, cardiopulmonary bypass, ischemic/reperfusion injury, gastritis, adult respiratory distress syndrome, cachexia, myocarditis, autoimmune disorders, eczema, psoriasis, heart failure, heart disease, atherosclerosis, dermatitis, urticaria, systemic lupus erythematosus, AIDS, AIDS dementia, chronic neurodegenerative disease, chronic pain, priapism, cystic fibrosis, amyotrophic lateral sclerosis, schizophrenia, depression, premenstrual syndrome, anxiety, addiction, migraine, Huntington's disease, epilepsy, neurodegenerative disorders, gastrointestinal motility disorders, obesity, hyperphagia, solid tumors, malaria, hematologic cancers, myelofibrosis, lung injury, graft-versus-host disease, head injury, CNS trauma, hepatitis, renal failure, liver disease, drug-induced lung injury, myasthenia gravis (MG), ophthalmic diseases, post-angioplasty, restenosis, angina or coronary artery disease.

14. A method for the treatment of an inflammatory condition mediated by nuclear factor kappa-B (NFκB), said method comprising administering to a subject in need thereof an effective amount of a therapeutic consisting essentially of a physiologically compatible compound which is readily hydrolyzable under selected physiological conditions to release carbon disulfide.

15. In a method for the treatment of a pathological condition employing a pharmacologically active agent therefor, the improvement comprising administering said pharmacologically active agent as part of a therapeutic consisting essentially of said pharmacologically active agent and carbon disulfide in a pharmaceutically acceptable carrier.

16. In a method for the treatment of a pathological condition employing a pharmacologically active agent therefor, the improvement comprising administering said pharmacologically active agent as part of a therapeutic comprising said pharmacologically active agent, a physiologically compatible compound which is readily hydrolyzable under selected physiological conditions to release carbon disulfide, and a pharmaceutically acceptable carrier therefor.

17. A composition consisting essentially of a physiologically compatible compound which is readily hydrolyzable under selected physiological conditions to release carbon disulfide, and a pharmaceutically acceptable carrier therefor.

18. A composition consisting essentially of carbon disulfide and a pharmaceutically acceptable carrier therefor.

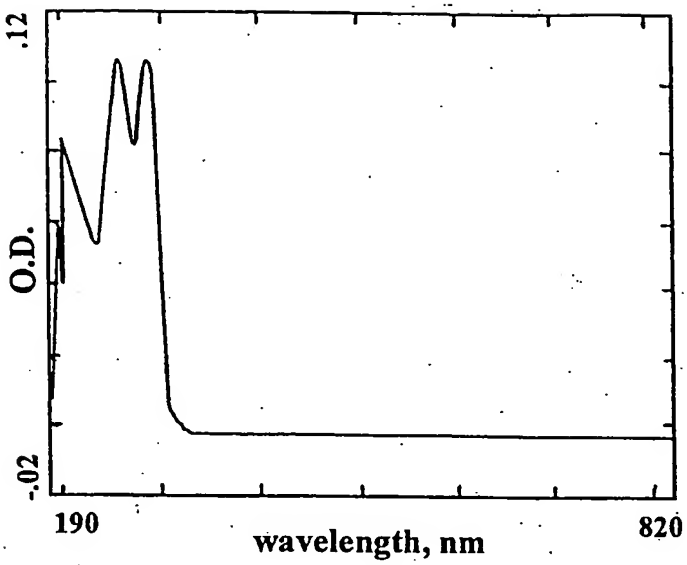


Fig. 1A

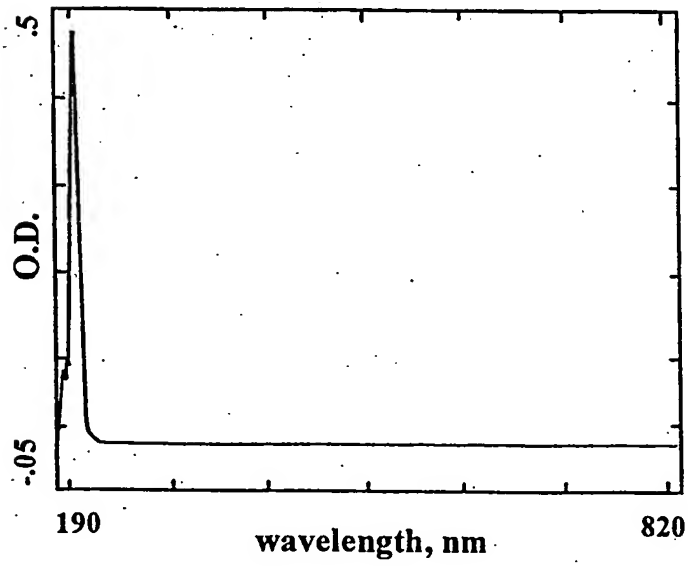
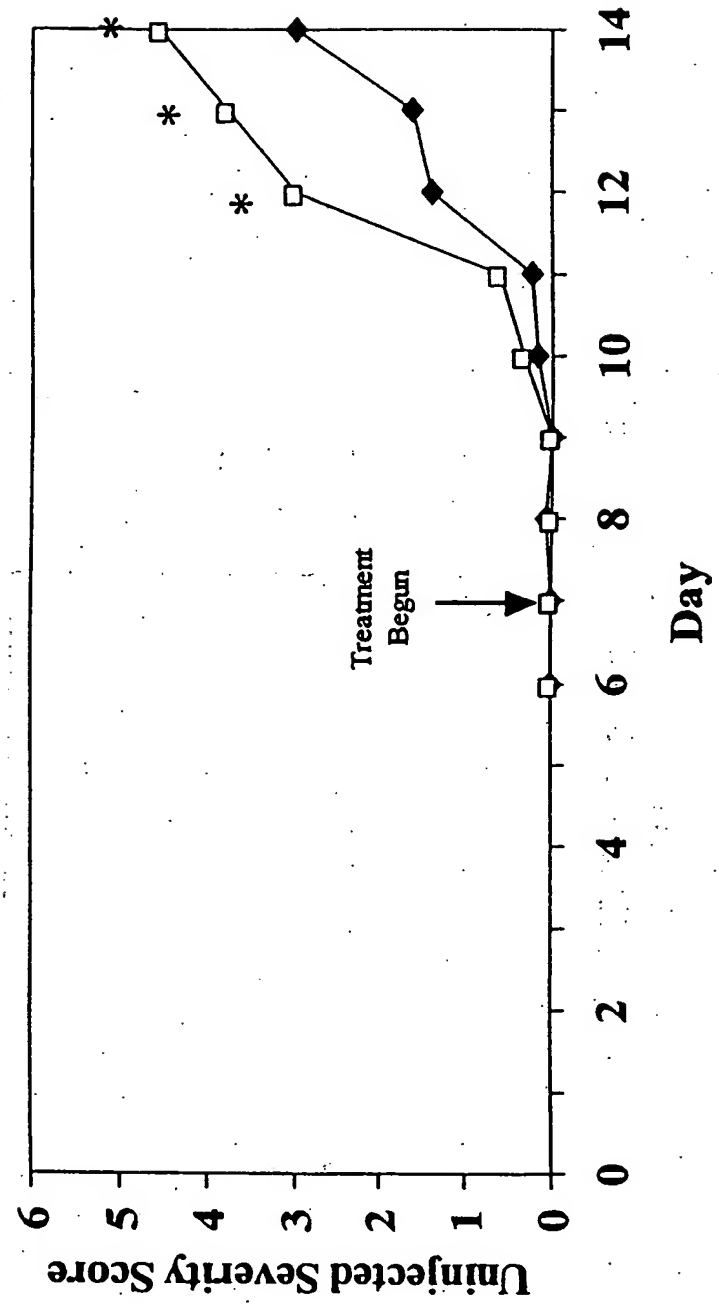


Fig. 1B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1
2
3
4
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0
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8
10
12
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Day
Treatment Begun
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FIGURE 2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/02679

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :A61K 31/13, 31/40, 31/195
US CL :514/423, 562, 655, 665
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/423, 562, 655, 665

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

REGISTRY, CAPLUS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,380,747 A (MEDFORD ET AL) 10 January 1995, columns 1-4.	1-18
X	Database HCAPLUS on STN (Columbus, OH, USA), No. 121:50038, STAAL, F. et al, 'Antioxidants inhibit stimulation of HIV transcription,' AIDS Res. Hum. Retroviruses, abstract, 1993, 9(4), pages 299-306.	1-18
X	Database HCAPLUS on STN (Columbus, OH, USA), No. 128:57286, NATHENS. A, et al, 'Pyrrolidine dithiocarbamate attenuates endotoxin-induced acute lung injury,' Am. J. Respir. Cell Mol. Biol., abstract, 1997, 17(5), pages 608-616.	1-18

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"B" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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